PATF''T COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

HARRISON GODDARD FOOTE
Belgrave Hall
Belgrave Street
Leeds LS2 8DD
ROYAUME-UNI

Date of mailing (day/month/year)
27 November 2001 (27.11.01)

Applicant's or agent's file reference
LPB/P32059WO

IMPORTANT NOTIFICATION

International application No.
PCT/GB00/03568

International filing date (day/month/year)
18 September 2000 (18.09.00)

1. The following indications appeared on record concerning:

☐ the applicant ☐ the inventor ☒ the agent ☐ the common representative

Name and Address
HARRISON GODDARD FOOTE
Tower House
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United Kingdom

State of Nationality

State of Residence

Telephone No.
+44 113 290 1400

Facsimile No.
+44 113 244 2829

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☐ the person ☐ the name ☒ the address ☐ the nationality ☐ the residence

Name and Address
HARRISON GODDARD FOOTE
Belgrave Hall
Belgrave Street
Leeds LS2 8DD
United Kingdom

State of Nationality

State of Residence

Telephone No.
+44 113 233 0100

Facsimile No.
+44 113 233 0101

Teleprinter No.

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☒ the International Preliminary Examining Authority
☐ the designated Offices concerned
☒ the elected Offices concerned
☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Facsimile No.: (41-22) 740.14.35

Authorized officer
Maria Victoria CORTIELLO

Telephone No.: (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
LPB/P32059WO		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/GB 00/ 03568	18/09/2000	17/09/1999
Applicant		
THE UNIVERSITY OF YORK		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language,** the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [X] furnished subsequently to this Authority in written form.

   [X] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [X] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 24-26, 30-32, 33

Present claim 33 relate to a compound defined by reference to a desirable characteristic or property, namely a drug or therapeutic agent identified, assessed or selected using a crystallised molecular complex of an E2NT protein or an E2NT crystal structure. The claim cover all compounds having this desirable characteristic or property, whereas the application does not provide support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

Although claims 24-26 could be, at least partially considered as mere presentation of information (Rule 39.1 (v) PCT / Art. 52(2d) EPC), and claims 30-32 at least partially as a computer program (Rule 39.1 (vi) PCT / Art. 52(2c) EPC), the search has been carried out as far as possible in our systematic documentation.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PC[redacted] 00/03568

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/025 C12N15/37 A61K39/12 A61K38/16 A61P31/20
A61P17/00 A61P35/00 G06F13/00 G06F9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 97 06246 A (VERTEX PHARMA) 20 February 1997 (1997-02-20) page 4, line 3 -page 5, line 6 page 6, line 22 -page 7, line 7 page 14, line 7 -page 16, line 2 page 17, line 12 -page 18, line 6 page 20, line 3 -page 28, line 30 & US 5 978 740 A 2 November 1999 (1999-11-02) --- -/--	1-33

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 March 2001	23/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Mateo Rosell, A.M.

3

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
Y	GAUTHIER J-M ET AL: "TWO DNA-BOUND E2 DIMERS ARE REQUIRED FOR STRONG TRANSCRIPTIONAL ACTIVATION AND FOR COOPERATION WITH CELLULAR FACTORS IN MOST CELLS" NEW BIOLOGIST, vol. 3, no. 5, 1991, pages 498-509, XP000989622 ISSN: 1043-4674 cited in the application abstract page 504, right-hand column, last line -page 506, right-hand column, last line ---	1-33
A	HARRIS SETH F ET AL: "Crystal structure of the human papillomavirus type 18 E2 activation domain." SCIENCE (WASHINGTON D C), vol. 284, no. 5420, 4 June 1999 (1999-06-04), pages 1673-1677, XP002162385 ISSN: 0036-8075 cited in the application the whole document ---	1,10,21, 22
A	HEGDE RASHMI S ET AL: "Crystal structure of the E2 DNA-binding domain from human papillomavirus type 16: Implications for its DNA binding-site selection mechanism." JOURNAL OF MOLECULAR BIOLOGY, vol. 284, no. 5, 18 December 1998 (1998-12-18), pages 1479-1489, XP002162386 ISSN: 0022-2836 cited in the application the whole document ---	1,10,21, 22
A	HEGDE RASHMI S ET AL: "Subunit rearrangement accompanies sequence-specific DNA binding by the bovine papillomavirus-1 E2 protein." JOURNAL OF MOLECULAR BIOLOGY, vol. 276, no. 4, 6 March 1998 (1998-03-06), pages 797-808, XP002162387 ISSN: 0022-2836 cited in the application the whole document --- -/--	1,10,21, 22

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	MCBRIDE A A ET AL: "E2 POLYPEPTIDES ENCODED BY BOVINE PAPILLOMAVIRUS TYPE 1 FORM DIMERS THROUGH THE COMMON CARBOXYL-TERMINAL DOMAIN TRANSACTIVATION IS MEDIATED BY THE CONSERVED AMINO-TERMINAL DOMAIN" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 86, no. 2, 1989, pages 510-514, XP000982632 1989 ISSN: 0027-8424 cited in the application the whole document ---	1-8
A	KNIGHT J D ET AL: "THE ACTIVATION DOMAIN OF THE BOVINE PAPILLOMAVIRUS E2 PROTEIN MEDIATES ASSOCIATION OF DNA-BOUND DIMERS TO FORM DNA LOOPS" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 88, no. 8, 1991, pages 3204-3208, XP000982633 1991 ISSN: 0027-8424 cited in the application the whole document ---	1-8
A	COOPER CHRISTOPHER S ET AL: "Identification of single amino acids in the human papillomavirus 11 E2 protein critical for the transactivation or replication functions." VIROLOGY, vol. 241, no. 2, 15 February 1998 (1998-02-15), pages 312-322, XP002162388 ISSN: 0042-6822 cited in the application abstract page 316, right-hand column, last line -page 319, left-hand column, line 1 ---	1,10
A	SAKAI HIROYUKI ET AL: "Targeted mutagenesis of the human papillomavirus type 16 E2 transactivation domain reveals separable transcriptional activation and DNA replication functions." JOURNAL OF VIROLOGY, vol. 70, no. 3, 1996, pages 1602-1611, XP002162389 ISSN: 0022-538X cited in the application the whole document --- -/--	1,10

3

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	YANG FAN ET AL: "Crystal structure of cyanovirin-N, a potent HIV-inactivating protein, shows unexpected domain swapping." JOURNAL OF MOLECULAR BIOLOGY, vol. 288, no. 3, 7 May 1999 (1999-05-07), pages 403-412, XP002162390 ISSN: 0022-2836 cited in the application the whole document ---	1,11-15, 17,18, 24,33
A	GHOSE A K ET AL : "DETERMINATION OF PHARMACOPHORIC GEOMETRY FOR COLLAGENASE INHIBITORS USING A NOVEL COMPUTATIONAL METHOD AND ITS VERIFICATION USING MOLECULAR DYNAMICS, NMR, AND X-RAY CRYSTAL" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY,US,AMERICAN CHEMICAL SOCIETY, WASHINGTON, DC, vol. 117, no. 16, 1995, pages 4671-4682, XP002051616 ISSN: 0002-7863 the whole document ---	1,11-20, 24-26,33
A	WIBLEY J E A ET AL: "A homology model of the three-dimensional structure of human O-6-alkylguanine-DNA alkyltransferase based on the crystal structure of the C-terminal domain of the Ada protein from Escherichia coli." ANTI-CANCER DRUG DESIGN, vol. 10, no. 1, 1995, pages 75-95, XP000989520 ISSN: 0266-9536 the whole document -& WIBLEY J E A ET AL.,: "erratum" ANTI-CANCER DRUG DESIGN, vol. 10, no. 1, 1995, page 439 XP002162457 ---	1-33
P,X	ANTSON ALFRED A ET AL: "Structure of the intact transactivation domain of the human papillomavirus E2 protein." NATURE (LONDON), vol. 403, no. 6771, 17 February 2000 (2000-02-17), pages 805-809, XP000926219 ISSN: 0028-0836 the whole document --- -/--	1-33

3

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	MEYERS THOMAS C ET AL: "Patent protection for protein structures and databases." NATURE STRUCTURAL BIOLOGY, vol. 7, no. Supplement, November 2000 (2000-11), pages 950-952, XP002162391 ISSN: 1072-8368 the whole document	1-33

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT[redacted]00/03568

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9706246 A	20-02-1997	US 5978740 A	02-11-1999
		AU 6766896 A	05-03-1997
		EP 0846163 A	10-06-1998
		JP 11511016 T	28-09-1999

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 March 2001 (29.03.2001)

PCT

(10) International Publication Number
WO 01/21645 A3

(51) International Patent Classification[7]: C07K 14/025, C12N 15/37, A61K 39/12, 38/16, A61P 31/20, 17/00, 35/00, G06F 13/00, 9/00

(21) International Application Number: PCT/GB00/03568

(22) International Filing Date:
18 September 2000 (18.09.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
GB9921938.8 17 September 1999 (17.09.1999) GB

(71) Applicant *(for all designated States except US)*: **THE UNIVERSITY OF YORK** [GB/GB]; Heslington Hall, York YO10 5DD (GB).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **ANTSON, Alfred** [GB/GB]; Department of Chemistry, University of York, York YO10 5DD (GB). **MAITLAND, Norman** [GB/GB]; Department of Biology, University of York, York YO10 5DD (GB).

(74) Agent: **HARRISON GODDARD FOOTE**; Tower House, Merrion Way, Leeds LS2 8PA (GB).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

(88) Date of publication of the international search report:
16 August 2001

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 01/21645 A3

(54) Title: TARGET FOR ANTIVIRAL THERAPY

(57) Abstract: A crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof, that comprises residues vital for viral transcription and/or replication. The invention also provides for the use of the dimer protein and interactions at its dimerisation surface in rationalised antiviral drug design.

INTERNATIONAL SEARCH REPORT

Int tional Application No
PCT/GB 00/03568

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07K14/025 C12N15/37 A61K39/12 A61K38/16 A61P31/20
A61P17/00 A61P35/00 G06F13/00 G06F9/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
9 March 2001	23/03/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl. Fax: (+31–70) 340–3016	Mateo Rosell, A.M.

3

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	WIBLEY J E A ET AL: "A homology model of the three-dimensional structure of human O-6-alkylguanine-DNA alkyltransferase based on the crystal structure of the C-terminal domain of the Ada protein from Escherichia coli." ANTI-CANCER DRUG DESIGN, vol. 10, no. 1, 1995, pages 75-95, XP000989520 ISSN: 0266-9536 the whole document -& WIBLEY J E A ET AL.,: "erratum" ANTI-CANCER DRUG DESIGN, vol. 10, no. 1, 1995, page 439 XP002162457	1-33
P,X	ANTSON ALFRED A ET AL: "Structure of the intact transactivation domain of the human papillomavirus E2 protein." NATURE (LONDON), vol. 403, no. 6771, 17 February 2000 (2000-02-17), pages 805-809, XP000926219 ISSN: 0028-0836 the whole document	1-33

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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T	MEYERS THOMAS C ET AL: "Patent protection for protein structures and databases." NATURE STRUCTURAL BIOLOGY, vol. 7, no. Supplement, November 2000 (2000-11), pages 950-952, XP002162391 ISSN: 1072-8368 the whole document	1-33

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 24-26, 30-32, 33

Present claim 33 relate to a compound defined by reference to a desirable characteristic or property, namely a drug or therapeutic agent identified, assessed or selected using a crystallised molecular complex of an E2NT protein or an E2NT crystal structure. The claim cover all compounds having this desirable characteristic or property, whereas the application does not provide support within the meaning of Article 6 PCT and disclosure within the meaning of Article 5 PCT. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the compound by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible.

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Information on patent family members

Int tional Application No
PCT/GB 00/03568

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9706246 A	20-02-1997	US 5978740 A	02-11-1999
		AU 6766896 A	05-03-1997
		EP 0846163 A	10-06-1998
		JP 11511016 T	28-09-1999

Target for Antiviral Therapy

The present invention provides a crystallised module of a nuclear phosphoprotein and an assay and method for determining interactions with human papillomavirus E2 for use in drug design, for use particularly but not exclusively in designing antiviral agents with potential use in treating warts, proliferative skin lesions and carcinoma of the cervix.

Background to the Invention

Human papillomaviruses (HPVs) cause warts and proliferative lesions in skin and other epithelia. In a minority of HPV types ("high risk", which include HPVs 16, 18, 31, 33, 45 and 56), further transformation of the wart lesions can produce tumours, most notably carcinoma of the cervix[1]. HPVs have evolved a sophisticated system of control, mediated by protein:DNA and protein:protein interactions, that involves both cellular and viral proteins. The 45 kDalton nuclear phosphoprotein, E2, has two central roles in this control. It acts as the principal virally encoded transcription factor and, in association with the viral E1 protein, it creates the molecular complex at the origin of the viral DNA replication[2].

E2 has three distinct modules. The N-terminal module (E2NT) of about 200 amino acids is responsible for interactions with viral and host cell transcription factors. It is followed by a flexible, proline-rich, linker module and a C-terminal module (E2CT), each of about 100 amino acids [3] (Fig. 1a). The E2CT binds as a homodimer to DNA sites with a consensus sequence of $ACCGN_4CGGT$ [4]. In most HPVs a long upstream regulatory region (URR) precedes the viral genes and contains four spatially conserved E2 binding sites: three sites proximal to the transcription start site (p97 in HPV16) and one approximately 500bp upstream.

The dimer of E2CT serves to anchor E2 protein to its recognition sites on the DNA, the function of the E2NT is to bind and localise at least three cellular transcription

factors, Sp1, TFIIB and AMF-1, to the transcription initiation complex. In addition, E2 interacts with another viral protein, E1, which has ATPase and helicase activities. E1 itself binds to the viral origin of replication which consists of about 100 bp and is surrounded by the three E2-binding sites, proximal to the transcription start. The E2:E1 interaction greatly increases the rate of HPV genome replication[2,5,6], Fig. 1a. An intact E2 is essential for the normal productive (wart) life cycle of HPV, however during malignant progression HPV DNA is integrated into the host cell genome, which usually results in disruption of the E2/E1 ORFs and loss of E2 protein, in turn leading to dysregulated expression of the viral oncogenes E6 and E7[7].

Consistent with its role as a transcription regulator, E2 has been shown to direct the formation of loops in DNA containing E2 binding sites[8]. The loops were only formed with intact E2, and not with the E2CT alone. The E2 binding sites did not function independently and their co-operative effect was mediated by full length E2, leading the authors to suggest that there were specific interactions mediated by E2 that bridged across the set of DNA binding sites through its N-terminal. A similar DNA loop structure could also be achieved with Sp1, a cellular transcription factor, which forms a complex with distally bound E2 [9]; Sp1/E2 interactions are critical for transcription activation in BPV[10].

Eighty six known E2 proteins from different species and different human subtypes[11] are highly conserved, with sequence identities typically of 35% in the N and C-terminal modules (Fig. 1b). The crystal structure of the E2CT has been determined both alone and in complex with cognate DNA[12-14]. The module is a dimer with a barrel fold, and induces substantial bending (42-44°) of the DNA from its B-form double helix[14].

The structure of the proteolytic fragment of HPV18 E2NT, missing 65 N-terminal residues, was recently reported at 2.1 Å spacing[15]. This allowed some analysis of mutational effects on function, although the missing 65 amino acids contain residues which are essential for the transcriptional and replication activities of the protein.

We report herein the structure of the complete E2NT determined by X-ray analysis at 1.9 Å. We have found that it is an L-shaped molecule with the residues vital for transcriptional and replication activities of the protein lying on opposite sides of the N-terminal domain. Surprisingly, our results show that the surface, vital for transcription activation, is in fact involved in association of two E2NT's into a dimer. We suggest that dimerisation of E2NT plays an important and key role in induction of DNA loop formation, the mechanism by which distally bound transcription factors would be brought close to the site of transcription initiation. More importantly, our results raise the possibility that dimer formation serves as a molecular switch between early gene expression and viral genome replication during HPV infection.

The process of rationalised drug design requires no explanation or teaching for the skilled person but a brief description is given here of computational design for the lay reader: various computational analyses are necessary to determine whether a molecule is sufficiently similar to the target moiety or structure. Such analyses may be carried out in current software applications, such as the Molecular Similarity application of QUANTA (Molecular Simulations Inc., Waltham, Mass.) version 3.3, and as described in the accompanying User's Guide, Volume 3 pages. 134-135.

The Molecular Similarity application permits comparisons between different structures, different conformations of the same structure, and different parts of the same structure. The procedure used in Molecular Similarity to compare structures is divided into four steps: 1) load the structures to be compared; 2) define the atom equivalences in these structures; 3) perform a fitting operation; and 4) analyze the results.

Each structure is identified by a name. One structure is identified as the target (i.e., the fixed structure); all remaining structures are working structures (i.e., moving structures). When a rigid fitting method is used, the working structure is translated and rotated to obtain an optimum fit with the target structure. The fitting operation uses a least squares fitting algorithm that computes the optimum translation and

rotation to be applied to the moving structure, such that the root mean square difference of the fit over the specified pairs of equivalent atom is an absolute minimum. This number, given in angstroms, is reported by QUANTA.

One skilled in the art may use one of several methods to screen chemical entities or fragments for their ability to associate with a target. Again, these methods require no elucidation for the skilled person but are described here for the benefit of the unskilled reader. The screening process may begin by visual inspection of the target on the computer screen, generated from a machine-readable storage medium. Selected fragments or chemical entities may then be positioned in a variety of orientations, or docked, within that binding pocket as defined supra. Docking may be accomplished using software such as Quanta and Sybyl, followed by energy minimization and molecular dynamics with standard molecular mechanics force fields, such as CHARMM and AMBER.

Specialized computer programs may also assist in the process of selecting fragments or chemical entities. These include:

1. GRID (P. J. Goodford, "A Computational Procedure for Determining Energetically Favorable Binding Sites on Biologically Important Macromolecules", J. Med. Chem., 28, pp. 849-857 (1985)). GRID is available from Oxford University, Oxford, UK.

2. MCSS (A. Miranker et al., "Functionality Maps of Binding Sites: A Multiple Copy Simultaneous Search Method." Proteins: Structure, Function and Genetics, 11, pp. 29-34 (1991)). MCSS is available from Molecular Simulations, Burlington, Mass.

3. AUTODOCK (D. S. Goodsell et al., "Automated Docking of Substrates to Proteins by Simulated Annealing", Proteins: Structure, Function, and Genetics, 8, pp. 195-202 (1990)). AUTODOCK is available from Scripps Research Institute, La Jolla, Calif.

4. DOCK (I. D. Kuntz et al., "A Geometric Approach to Macromolecule-Ligand Interactions", J. Mol. Biol., 161, pp. 269-288 (1982)). DOCK is available from University of California, San Francisco, Calif.

Once suitable chemical entities or fragments have been selected, they can be assembled into a single compound or complex. Assembly may be preceded by visual inspection of the relationship of the fragments to each other on the three-dimensional image displayed on a computer screen in relation to the structure coordinates of calcineurin. This would be followed by manual model building using software such as Quanta or Sybyl.

Useful programs to aid one of skill in the art in connecting the individual chemical entities or fragments include:

1. CAVEAT (P. A. Bartlett et al, "CAVEAT: A Program to Facilitate the Structure-Derived Design of Biologically Active Molecules". In Molecular Recognition in Chemical and Biological Problems", Special Pub., Royal Chem. Soc., 78, pp. 182-196 (1989)). CAVEAT is available from the University of California, Berkeley, Calif.

2. 3D Database systems such as MACCS-3D (MDL Information Systems, San Leandro, Calif). This area is reviewed in Y. C. Martin, "3D Database Searching in Drug Design", J. Med. Chem., 35, pp. 2145-2154 (1992).

3. HOOK (available from Molecular Simulations, Burlington, Mass.).

As the skilled reader will already know, instead of proceeding to build ligand for the target in a step-wise fashion, one fragment or chemical entity at a time as described above, inhibitory or other target-binding compounds may be designed as a whole or *de novo*. These methods include:

1. LUDI (H.-J. Bohm, "The Computer Program LUDI: A New Method for the De Novo Design of Enzyme Inhibitors", J. Comp. Aid. Molec. Design, 6, pp. 61-78 (1992)). LUDI is available from Biosym Technologies, San Diego, Calif.

2. LEGEND (Y. Nishibata et al., Tetrahedron, 47, p. 8985 (1991)). LEGEND is available from Molecular Simulations, Burlington, Mass.

3. LeapFrog (available from Tripos Associates, St. Louis, Mo.).

Other molecular modelling techniques may also be employed. See, e.g., N. C. Cohen et al., "Molecular Modeling Software and Methods for Medicinal Chemistry, J. Med. Chem., 33, pp. 883-894 (1990). See also, M. A. Navia et al., "The Use of Structural Information in Drug Design", Current Opinions in Structural Biology, 2, pp. 202-210 (1992).

Once a compound has been designed or selected by the above methods, the efficiency with which that entity may bind to a target may be tested and optimized by computational evaluation. For example, an effective ligand will preferably demonstrate a relatively small difference in energy between its bound and free states (i.e., a small deformation energy of binding). Thus, the most efficient ligands should preferably be designed with a deformation energy of binding of not greater than about 10 kcal/mole, preferably, not greater than 7 kcal/mole. Ligands may interact with the target in more than one conformation that is similar in overall binding energy. In those cases, the deformation energy of binding is taken to be the difference between the energy of the free entity and the average energy of the conformations observed when the inhibitor binds to the protein.

An entity designed or selected as binding to a target may be further computationally optimized so that in its bound state it would preferably lack repulsive electrostatic interaction with the target enzyme. Such non-complementary (e.g., electrostatic) interactions include repulsive charge-charge, dipole-dipole and charge-dipole

interactions. Specifically, the sum of all electrostatic interactions between the inhibitor or other ligand and the target, when the inhibitor is bound to the target, preferably make a neutral or favourable contribution to the enthalpy of binding.

Specific computer software is available in the art to evaluate compound deformation energy and electrostatic interaction. Examples of programs designed for such uses include: Gaussian 92, revision C [M. J. Frisch, Gaussian, Inc., Pittsburgh, Pa. .COPYRGT.1992]; AMBER, version 4.0 [P. A. Kollman, University of California at San Francisco, .COPYRGT.1994]; QUANTA/CHARMM [Molecular Simulations, Inc., Burlington, Mass. .COPYRGT.1994]; and Insight II/Discover (Biosysm Technologies Inc., San Diego, Calif. .COPYRGT.1994). These programs may be implemented, for instance, using a Silicon Graphics workstation, IRIS 4D/35 or IBM RISC/6000 workstation model 550. Other hardware systems and software packages will be known to those skilled in the art.

Once the ligand has been optimally selected or designed, as described above, substitutions may then be made in some of its atoms or side groups in order to improve or modify its binding properties. Generally, initial substitutions are conservative, i.e., the replacement group will have approximately the same size, shape, hydrophobicity and charge as the original group. It should, of course, be understood that components known in the art to alter conformation should be avoided. Such substituted chemical compounds may then be analyzed for efficiency of fit to a calcineurin-like binding pocket by the same computer methods described in detail, above. Again, all these facts are familiar to the skilled person.

Another approach is the computational screening of small molecule data bases for chemical entities or compounds that can bind in whole, or in part, to a target. In this screening, the quality of fit of such entities to the binding site may be judged either by shape complementarity or by estimated interaction energy. E. C. Meng et al., J. Comp. Chem., 13, pp. 505-524 (1992).

The computational analysis and design of molecules, as well as software and computer systems therefor are described in US Patent No 5,978,740 which is included herein by reference, including specifically but not by way of limitation the computer system diagram described with reference to and illustrated in Fig 3 thereof as well as the data storage media diagram described with reference to and illustrated in Fig 4s and 5 thereof.

Statement of the Invention

According to a first aspect of the invention there is provided a crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof, for use in rationalised drug design. We have found that the dimer comprises residues vital for transcriptional and replicational activities of said protein lying on opposite sides of an N-terminal domain, for use in rationalised drug design.

Preferably the E2NT dimer protein is substantially as depicted in any of Figures 2c and/or 3a-d.

According to a second aspect of the invention there is provided an *in vitro* method for identifying and/or selecting a candidate therapeutic agent, the method comprising determining interaction of a E2 N-terminal module (E2NT) dimer in a sample by contacting said sample with said candidate therapeutic agent and measuring DNA loop formation.

Preferably, the method is for use in identifying and/or selecting an antiviral candidate therapeutic agent.

Preferably, the candidate therapeutic agent interferes or blocks interactions of E2NT so as to interfere or block viral and/or cellular transcription factors.

According to a third aspect of the invention there is provided use of an E2NT dimerisation inhibitor in the preparation of a medicament for use in treating warts, proliferative skin lesions and/or cervical cancer.

According to a fourth aspect of the invention there is provided a method of monitoring the efficacy of an antiviral therapy in a patient receiving a medicament for the treatment of warts, proliferative skin lesions and/or cervical cancer comprising taking a sample from said patient and measuring E2NT interactions and/or DNA loop formation.

Thus it will be appreciated that a patient can be monitored at the start of therapy to test its effectiveness. Alternatively, a patient can be monitored once a therapy has been established so as to monitor its efficacy with a view to altering a therapy if found to be unsatisfactory.

The human papillomavirus E2 protein controls the primary transcription and replication of the viral genome. Both activities are governed by a ~200 amino acid N-terminal module (E2NT) which is connected to a DNA binding C-terminal module by a flexible linker. The crystal structure of the E2NT module from high-risk type 16 human papillomavirus reveals an L-shaped molecule with two closely packed domains, each with a novel fold. It forms a dimer in the crystal and in solution. The dimer structure is important in the interactions of E2NT with viral and cellular transcription factors and is the key to induction of DNA loops by E2. These loops may serve to target distal DNA-binding transcription factors to the region proximal to the start of transcription. The structure has implications for antiviral drug design and cervical cancer therapy.

The invention includes method for identifying and/or selecting a candidate therapeutic agent, comprising applying rationalised drug design to a crystal structure obtainable by crystallising E2NT, cryogenically freezing the crystals and generating the crystal structure using X-ray diffraction. The method by which the E2NT crystal

structure is obtainable may comprise crystallisation using hanging-drop vapour diffusion. The method by which E2NT crystal structure is obtainable may comprise X-ray diffraction using uranium acetate and gold cyanide E2NT derivatives and refining with data extending to 1.9 Å spacing. The crystal structure may comprise the portions of amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94. The rationalised drug design may comprise designing drugs which interact with the dimerisation surface of E2NT.

Further provided is a computer for producing a three-dimensional representation of a molecule or molecular complex, wherein said molecule or molecular complex comprises or a three-dimensional representation of a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å , wherein said computer comprises:

(a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises the structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3;

(b) a working memory for storing instructions for processing said machine-readable data;

(c) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said three-dimensional representation; and

(d) a display coupled to said central-processing unit for displaying said three-dimensional representation.

In class of embodiments, the three-dimensional representation is of a molecule or molecular complex is defined by the set of structure coordinates according to Table 3, or wherein said three-dimensional representation is of a homologue of said molecule or molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

An additional aspect of the invention resides in a computer for determining at least a portion of the structure coordinates corresponding to an X-ray diffraction pattern of a molecule or molecular complex, wherein said computer comprises:

(a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises at least a portion of the structural coordinates according to Table 3;

(b) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises an X-ray diffraction pattern of said molecule or molecular complex;

(c) a working memory for storing instructions for processing said machine-readable data of (a) and (b);

(d) a central-processing unit coupled to said working memory and to said machine-readable data storage medium of (a) and (b) for performing a Fourier transform of the machine readable data of (a) and for processing said machine readable data of (b) into structure coordinates; and

(e) a display coupled to said central-processing unit for displaying said structure coordinates of said molecule or molecular complex.

A yet further aspect of the invention relates to a crystallised molecule or molecular complex comprising a dimerisation surface defined by structure coordinates of E2NT

amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å. The molecule or molecular complex may be defined by the set of structure coordinates according to Table 3, or a homologue thereof, wherein said homologue has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

27. A machine-readable data storage medium (e.g. a magnetic or optical storage medium, for example a hard disc, a floppy disc or a CD-ROM), comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of a molecule or molecular complex comprising a dimerisation surface defined by structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3, or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

In the machine-readable data storage medium the molecule or molecular complex may be defined by the set of structure coordinates according to Table 3, or a homologue of said molecule or molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

The invention further provides a machine-readable data storage medium comprising a data storage material encoded with a first set of machine readable data which, when combined with a second set of machine readable data, using a machine programmed with instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second

set of machine readable data, wherein: said first set of data comprises a Fourier transform of at least a portion of the structural coordinates according to Table 3; and said second set of data comprises an x-ray diffraction pattern of a molecule or molecular complex.

In another aspect, the invention resides in a method for evaluating the ability of a chemical entity to associate with a molecule or molecular complex according to the invention, comprising the steps of:

a. employing computational means to perform a fitting operation between the chemical entity and a dimerisation surface of the molecule or molecular complex; and

b. analysing the results of said fitting operation to quantify the association between the chemical entity and the dimerisation surface.

Detailed Description f the Invention

The invention will now be described by way of example only with reference to the following Figures and Tables wherein:

Table 1 illustrates X-ray data and phasing statistics;

Table 2 illustrates refinement and model correlation;

Table 3 shows the structure coordinates of the E2NT module;

Figure 1a represents functional assignments of HPV 16 E2 protein;

Figure 1b illustrates sequence alignment of E2NT modules from a subset of HPV types;

Figure 2a illustrates a stereo view of electron density with a final model at the dimer interface of the E2NT module, viewed down the crystallographic two-fold axis;

Figure 2b represents a stereo ribbon diagram of the E2NT module;

Figure 2c represents the E2NT dimer;

Figure 3a illustrates a schematic view of URR;

Figure 3b illustrates a schematic view of loop formation induced by binding of E2 proteins to two cognate sites;

Figure 3c illustrates a model of E2 dimer formation;

Figure 3d illustrates loops within URR as shown in Figure 3b;

Figure 4a illustrates the distribution of conserved residues on the E2NT monomer;

Figure 4b illustrates a first cluster of conserved residues on the E2NT monomer;

Figure 4c illustrates a second cluster of conserved residues on the E2NT monomer; and

Figure 4d illustrates conserved residues Gln12 and Glu39.

Those of skill in the art understand that a set of structure coordinates for an enzyme or an enzyme-complex or a portion thereof, is a relative set of points that define a shape in three dimensions. Thus, it is possible that an entirely different set of coordinates could define a similar or identical shape. Moreover, slight variations caused by acceptable errors in the individual coordinates will have little, if any effect on overall shape. In terms of binding pockets, these acceptable variations would not be expected to alter the nature of ligands that could associate with those pockets.

The term "associating with" refers to a condition of proximity between a chemical entity or compound, or portions thereof, and a calcineurin molecule or portions thereof. The association may be non-covalent--wherein the juxtaposition is energetically favored by hydrogen bonding or van der Waals or electrostatic interactions--or it may be covalent.

The invention is also described with reference to US Patent No 5,978,740 which is included herein by reference, including specifically but not by way of limitation the computer system diagram described with reference to and illustrated in Fig 3 thereof as well as the data storage media diagram described with reference to and illustrated in Fig s 4 and 5 thereof.

With reference to Figure 1a and functional assignments of E2. There is shown in a schematic view of NT, linker and CT modules of E2 indicating known functions of each module. Amino acid numbers which delimit the modules correspond to E2 from HPV16. In Figure 1b, there is shown the sequence alignment of the E2NT modules from a subset of HPV types (HPV16, HPV18, HPV11 and HPV2a) and one BPV type. Shaded blocks above the alignment indicate the experimentally determined secondary structure. Shaded blocks below the sequences indicate the minimal peptide sequences involved in protein:protein interactions, suggested by mutation studies. Residues with more than 90% identity among 86 PV types are coloured: red for internal structural residues, green for residues within the fulcrum region, blue for surface residues.

With reference to the structural features of E2, in Figure 2a there is shown a stereo view of the electron density with the final model, at the dimer interface of the E2NT module, viewed down the crystallographic two-fold axis. The likelihood weighted map is contoured at the 1.5 σ level. Ribbons of two independent monomers are coloured blue and yellow. Side chains of ARG37 and Ile73 which are known to be critical for transactivation [4,31], are shown in dark green; side chain of other residues at the dimer interface are shown in light green. Oxygen atoms are in red, nitrogen in blue, water molecules are shown as orange spheres and hydrogen bonds as dashed sticks. In Figure 2b, there is shown a stereo ribbon diagram of the E2NT module. The N1 domain is shown in aquamarine and the N2 domain in pink, with the fulcrum in green. In Figure 2c, there is shown the dimer of E2NT, showing the extent of the interface between the two subunits. The view is as in Figure 2a but rotated clockwise by 90°. Side chains of Gln12 and Glu39 which are critical for interactions with E1 [31-33,37] are shown in magenta. Side chains of residues at the dimer interface are coloured as per Figure 2a.

With reference to Figures 3a-d there is shown loop formation in the URR of HPV16. In Figure 3a, there is shown a schematic view of the URR. The four E2-binding sites are represented by boxes. Numbers in italics indicate distances between individual

sites upstream of the p97 promoter. Two possible E2 configurations, with separate or dimeric E2NT modules are shown. In Figure 3b, there is shown a schematic view of loop formation induced by binding of E2 proteins to two cognate sites, based on the experiments reported by Knight *et al*[8]. In Figure 3d, there is shown the possible DNA loops within the URR as depicted in Figure 3b. In Figure 3c, there is shown a model of the formation of E2 dimers, showing interactions between both the C-terminal and E2NT modules. The C-terminal dimer, with its bound DNA, is based on the crystal structure of this module[12]. The E2NT dimer is proposed from the present work. The relative orientation and position of the E2NT and C-terminal modules is purely schematic.

With reference to Figures 4a-d there are shown functionally important residues. In Figure 4a, there is shown the distribution of conserved residues on the E2NT monomer. In Figures 4b and 4c there is shown the two clusters of conserved residues in the fulcrum of E2NT. In Figure 4d, there are shown conserved residues Gln12 and Glu39. Bonds in ball-and stick models are coloured aquamarine (N1 domain), pink (N2 domain) and green (fulcrum). Hydrogen bonds are shown as dashed lines, water molecules as orange spheres, oxygen atoms are in red, nitrogen atoms in blue and sulphur atoms in yellow.

There is convincing evidence that the E2 protein has an extended structure, is flexible and that its functions depend on this property. This is probably the reason why the intact protein has not yet been crystallised in spite of intensive efforts. A major problem is the extended flexible linker module, with around 100 residues. E2NT proved difficult to crystallise, and a number of different constructs were made and overexpressed before crystallisation with residues 1 to 201 was achieved, but even this construct possessed limited stability. The protein had to be crystallised within 2-3 days of purification; crystals grew within about 48 hours but only retained useful diffraction quality for a further 2-3 days. This necessitated that crystals be rapidly vitrified in cryoprotectant buffer and stored for use as soon as detector time became available[16].

Crystals of E2NT belong to the space group $P3_121$ with unit-cell dimensions a=b=54.3 Å, c=155.5 Å. The structure was determined using two heavy atom derivatives and refined with data extending to 1.9 Å spacing (Fig. 2a). The main chain is well defined throughout with the exception of residues 125 and 126 which are in an exposed loop and are mobile. There was density for the last residue of the His-tag at the N-terminus, but none for the remainder of this entity. All amino acids lie in the allowed regions of the Ramachandran (ϕ,ψ) plot[17] with 92.4% in most favoured regions[18].

The transactivation module is composed of two domains, N1 and N2, arranged so as to give it an overall L-shaped appearance. Analysis of the PDB[19]using DALI[20]shows that both have unique organisation of their secondary structures. Domain N1, which forms the N-terminus of the intact E2, is composed of residues 1 to 92, which fold into three long α-helices, Figure 2 (b,c). There is a tight loop between α1 and α2 and a more extended one between α2 and α3. The three helices pack antiparallel to one another in the form of a twisted plane, with angles of about 20° and 25° between the pairs of consecutive helices. DALI indicated a maximum Z-score of 5.7, that could suggest a significant correlation, for colicin 1a, a membrane protein which contains three 80 Å long α-helices arranged more or less coplanar[21]. This is the only other known protein that contains a true domain made up of such a packing of three helices. In addition there were 42 other structures which gave Z-scores above 4.0, most of which were four helix bundles, such as bacterioferritin[22]. However, in these only two of the three N1 helices superimposed simultaneously on two, not always adjacent, bundle helices as a result of a more planar arrangement of helices within N1. The indications are that the similarities observed reflect the optimum stacking angle of antiparallel helices against one another rather than suggesting a common ancestor for the evolution of these molecules.

Domain N2 is made up of residues 110 to 201 and is composed almost entirely of antiparallel β structure, with only one short helical segment from residues 171 to 178,

Figure 2 (b,c). The secondary structure has two short three and four stranded antiparallel β pleated sheets interconnected by two stranded β ribbons. For this domain DALI failed to identify any significant homologies to known structures, with a highest Z-score of only 2.1. From the analysis of Harris and Botchan[15] and the present study, the N2 fold appears to be novel.

The structure between the N1 and N2 domains (residues 93 to 109) contains two consecutive single turns of helical structure, resulting in a compact and tight turn. It packs closely against elements of both domains and is not a truly independent structural domain. Rather it forms a fulcrum in the L-shape formed by N1 and N2 where it could act as a hinge, allowing the two domains to change their relative conformation in a specific way. Several of the interactions between adjacent regions of chain in the fulcrum are mediated indirectly through H-bonds involving water molecules, suggesting the possibility of flexibility.

One of the most striking features of the crystal structure is the association of two E2NT monomers into a tight dimer. The two E2NT monomers pack around the crystallographic 2-fold axis, as shown in Figure 2a. The dimer interface is formed mostly by amino acids from helices α2 and α3 of the N1 domain and by residues 142-144 from the N2 domain. The total buried surface area between the two E2NT is 2026 $A^{\circ 2}$, comparable to the 2444 $A^{\circ 2}$ buried between the two E2CT[12], which are known to form a tight dimer with a K_d of 3-6 x 10^{-8} M [23,24].

In the E2NT dimer interface, each subunit contributes a cluster of seven equivalent residues, invariant or conserved in the 86 known sequences of E2[11], with many direct and water-mediated hydrogen bonds and rather few non-polar contacts, Fig. 2. Analysis of the dimer forming surfaces shows that all the direct hydrogen bonds between monomers are made through these seven amino acids. For the invariant Arg37, all possible side-chain hydrogen bonds are made and all are well defined, Figure 2. Three of them are across the dimer interface. One hydrogen bond is critical, from NH2 to the main chain carbonyl oxygen of Leu77. A second hydrogen bond from NH2 is to OG1 of Thr81; in five out of 86 sequences this residue is

glutamine, and modelling shows a hydrogen bond is possible to the NE of Arg37. The NH1 of Arg71 H-bonds to the OE1 of residue 80, which is Glu or Gln in all but six variants. At the NE of Arg37 there is an ideal H-bond to water that itself makes another strong H-bond across the dimer interface to the main-chain carbonyl oxygen of residue 142. The role of the invariant Ile73 is the filling of the intersubunit non-polar volume made up of the aliphatic parts of Arg37, Gln76 and of Leu77 - in this case from both monomers. The Leu77 is in a few sequences substituted by valine or isoleucine and in 9 out of 86 known sequences by methionine. Inspection of the structure shows that Leu77 is partially exposed to the solvent and therefore different hydrophobic side chains could be easily accommodated at this site. Another important non-polar side chain is Ala69. Its side chain methyl packs into the surface of the other monomer at van de Waals distance from the main chain of residue 142. The only observed mutation of Ala69 is to Gly, and is easily accommodated. Gln76 is conserved or has homologous substitutions in about 2/3 of E2 sequences; in about 1/4 of the sequences there is methionine or valine at this position[11]. Although hydrophobic substitutions of Gln76 would disrupt the hydrogen bonding to Glu80 across the dimer interface, and to Arg37 from the same subunit, the hydrophobic side chain at residue 76 could instead make a compensating hydrophobic interaction with the adjacent intersubunit hydrophobic pocket formed by Ile73 and Leu77.

Modelling of the amino acid variations in the 86 known papillomavirus E2 proteins into the other contacts at the dimer interface shows that they generally can be accommodated (data not shown). The consistency of the hydrogen bonds and van de Waals contacts at the monomer-monomer interface in the various sequences suggests therefore that the E2NT dimer interactions are potentially present in all papillomaviruses.

The first experimental evidence for the E2NT dimerisation in the presence of DNA with multiple E2-binding sites was provided by Knight *et al* in 1991[8]. Their studies showed that intact E2 led to the formation of DNA loops on templates with widely separated E2 binding sites, while a truncated E2, containing the DNA-binding E2CT but missing the N-terminal 161 residues, did not. Such dimerisation is further

supported by the observed synergistic transcription activation by a complex of two DNA-bound E2 dimers[25].

To analyse the functional behaviour of the E2NT dimers further, we measured the dissociation constant by sedimentation equilibrium using analytical ultracentrifugation of recombinant E2NT protein containing the 201 N-terminal amino acids. A value of $K_d = 8.1 \pm 4 \times 10^{-6}$ M was obtained, indicating medium-strength association. The micromolar range of the E2NT dimer K_d is certainly physiologically significant, and compares well with values for other transcription factors which have relatively low dissociation constants, often with the K_d values between 1 μM and 20 μM [26,27]. *In vivo*, the interaction could be enhanced when the two E2NT modules are placed in close proximity. Indeed, E2CT forms dimers which bind to the multiple DNA-binding sites located within the URR of viral DNA with K_d of protein:DNA interactions usually in the nanomolar range[28]. Consequently, the local concentration of E2NT, bound to the E2CT via the non-conserved, flexible ~80 amino-acid linker, is effectively increased.

E2NT dimer interactions, as seen in the crystal structure, could form either between modules which are already part of a single E2 dimer, formed as a result of E2CT dimerisation interactions and bound to a single E2 binding site on the DNA (Fig. 3a), or between two preformed E2 dimers located on different E2 binding sites (Fig. 3b). The results of the electron microscopy suggest that the latter dimerisation does occur[8]. Although no direct experimental evidence exists for the former dimerisation, it does also seem possible due to the flexibility of the linker connecting the two modules. We propose that E2 molecules may initially keep their N-terminal modules within their internal dimers, but swap N-terminal modules and cross link to E2 molecules bound to distant DNA binding sites to form active loop structures during transcriptional activation and / or HPV DNA replication (Figure 3d). As discussed below, the effects of mutations on transcriptional transactivation can be explained in terms of the dimer being an essential element in this process.

E2 is a regulator of both transcription and viral DNA replication and thus interacts with other viral and host macromolecules in the infected cell. Indication of the possible importance of individual residues in the function comes firstly from the structure, secondly from the extensive set of sequences of the papillomaviral E2's and thirdly from mutagenesis studies on the individual proteins. In the following we make a primary attempt to map the molecule's function onto its structure.

The pattern of amino acid conservation for the 86 available papilloma sequences[11] has been analysed using the GCG program suite[29]. The sequences exhibit striking variation, characteristic of some virus families. However, 33 of the total 201 residues in the E2NT construct were totally or highly conserved. Fig. 4a illustrates the distribution of these 33 residues in the dimer. These were categorised into two sets: those with an essentially structural role and those exposed on the surface with a potential for intermolecular interactions. Thirteen residues (Fig. 1b) are buried or play a purely structural role within the monomer, they are not expected to be of functional importance and will not be discussed here.

A further 12 of these 33 residues stand out as having a structural role in the interface of the N1 and N2 domains. They form three clusters, the first making direct interactions between the two domains (Ile82, Glu90, Trp92, Lys112, Tyr138, Val145) and two separate sets of interactions, one from N2 (Pro106, Lys111, Phe168, Trp134) and the other from N1 (Trp33, Leu94) to the structure connecting them, referred to here as a fulcrum. The first two clusters are shown in Figure 4 b, c and it can be seen that Lys111 and Lys112 play key roles. Their side chains point in opposite directions to one another and their terminal amino groups are involved in near ideal patterns of hydrogen bonds. The flat surfaces of their extended side chains stack against Trp134 and Trp92, respectively. This clustering of invariant residues at the interface indicates a functional importance for the relative orientation of N1 and N2. The fulcrum could indeed provide a flexible pivot between the two domains, but there is no direct evidence for this as yet. Finally, while the side chain of Glu90 is held tightly in place by two H-bonds and could have a structural role, its OE2 atom is

exposed on the surface and is surrounded by near invariant side-chains, which may thus play a part in interactions with other molecules.

Of the remaining eight conserved residues, mutational substitutions of Glu20, Glu100 and Asp122 [30-33] had moderate effects on the transactivation and replication properties of E2, which depended on a particular viral strain. Glu20 lies on the top surface of N1. Asp122 lies far away on the distal surface of N2. Glu100 is completely exposed and points into the solvent at the junction of the L between the N1 and N2 domains. The functional role of these amino acids has yet to be clarified.

Three conserved amino acids (Arg37, Glu39 and Ile73) have been subjected to point mutation and the effects on the two principal functions of E2, i.e. transactivation and HPV DNA replication have been assessed (reviewed in[4],also [31,34,35]). Together with the remaining two conserved amino acids, Gln12 and Ala69, these residues form two functionally important surfaces (see below).

Finally, a number of the mutational results (reviewed in [4], also [31,34,35]) correspond to residues that can be assigned to structural roles. Substitution of these residues will lead to substantial conformational changes and a probable inability to fold correctly. This is particularly true for some of the deletion mutants involving the core of the molecule. Knowledge of the structure will allow a more rational choice and design of mutants in the future.

The induction of DNA loops by E2NT dimerisation could be important for the construction of the active transcription bubble by targeting DNA-binding transcription factors, bound at distal sites, to the region proximal to the start of transcription (reviewed in [36]). In support of this, residues Arg37, Ile73 and Gln76 map onto the surface of E2NT involved in dimer formation, and mutations result in considerable disruption of transactivation, while having little effect on replication, [4,15,31]. The structure also shows that Ala69 which points its side chain methyl across the dimer interface, is also critical for transactivation. Mutational substitutions to

amino acids with longer side chains should have a knock out effect on E2NT dimer formation and consequently on transactivation.

The sites of association with cellular transcription factors AMF-1 (residues 74-134) and TFIIB (134-216) were previously mapped onto the E2NT module (Figure 1) using a series of deletion mutants as well as point mutations[34,35]. These sites were mutually exclusive. In the structure, residues 74-134 include the fulcrum, while residues 134-216 correspond to domain N2. Further biochemical and structural studies can now be planned to characterise these interactions in more detail.

Replication of the viral genome is initiated by binding of another viral protein, E1, to the origin of DNA replication[4] which is itself flanked by two E2 binding sites, Fig. 3a. While the function of E2CT dimers is to bind specifically to the DNA sites, E2NT interaction with E1 enhances the binding of E1 to this region. Mutational substitutions of Glu39 generally retained transcriptional activation while DNA replication was substantially reduced[31-33,37]. In the structure, the conserved Glu39 makes every possible hydrogen bond by its side chain carboxyl oxygens, Fig. 4d. One hydrogen bond is to NE2 of Gln12, which is absolutely conserved in all known sequences of E2. The other three hydrogen bonds are to the water molecules which are part of an intimate net of well-defined water molecules surrounding Glu39 and mediating its interactions with adjacent residues. Interestingly, a number of these protein interactions with water molecules are conserved as they are made to the protein backbone, including carbonyl oxygens of Gln12, Met36 and Lys68. While mutation of Gln12 in BPV1 only slightly affected both transactivation and replication, it substantially reduced cooperative origin binding[30,32]. The close positioning of Gln12 and Glu39 in the three-dimensional structure further enhances the notion that these two resides are involved in interactions with E1. The conserved set of interactions at Gln12/Glu39 suggests that the main chain carbonyl oxygens of Gln12 and Met36 and the conserved water molecules could be also involved in these interactions. Gln12/Glu39 are surrounded by Leu8, Ile15, Met36, Tyr43, Gln57 and

Lys68, which are unlikely to contribute into E2/E1 interactions, as these residues are not well conserved in E2 sequences from different papillomaviruses.

The Gln12/Glu39 cluster lies on a side of the N1 domain which is opposite to the side involved in transactivation (and dimerisation), Figure 2c. Notably, the spatial separation of the two functionally important surfaces suggests that E2NT module could be able to interact with E1 at the same time as it interacts through the dimerisation interface with another E2NT module.

The structure reported here for the entire E2 transactivation module, has several implications for understanding of E2 function. It is now possible to map known mutations onto the E2 three-dimensional structure, and to use the knowledge of amino acid conservation and the effects of mutations to assign roles in folding, structure and function to residues. To this end, our results indicate that molecular surfaces involved in transactivation and E1-binding are located at opposite sides of the N1 domain of E2NT, suggesting that both surfaces could be accessed simultaneously by other protein factors. In line with these observations, E1 has been shown to modulate transactivation by directly interacting with E2, leading to repression of transactivation in the presence of excess E1[38]. It is not inconceivable that the docking of E2NT dimer with E1 is sufficient to block further association with other target proteins.

The structure shows that the transactivation surface is involved in the formation of the E2NT dimer, which could cross-link E2 molecules bound by their E2CT modules to well-separated DNA sites. Inevitably, such dimerisation would cause DNA to form a loop structure, targeting distally bound transcription factors to regions close to the promoter. While this process has been suggested to be essential for transactivation[36], the definition of interacting surfaces between E2 and other cellular transcription factors requires a great deal of further study.

Our results suggest that the process of DNA loop formation could involve swapping of E2NT modules across E2 dimers bound at separated DNA sites (Fig. 3a-d). The polar components of the monomer-monomer interactions may favour such exchange. Domain swapping is a well-recognised phenomenon that occurs relatively frequently between two individual monomers containing domains connected by a flexible linker [39,40]. E2 is to our knowledge the first example where the swapping event is predicted to occur between dimers.

The dimerisation surface of E2 represents a good target for designing anti-viral drugs, since it is essential for viral transcription, there is no homologous human protein and the residues forming the interface are highly conserved among different viral strains. Dynamic interactions between transcription factors play a central role in the regulation of transcription and replication. Dimerisation, heterodimerisation and the monomer-to-dimer transition may play important roles during the control of the papillomavirus life cycle. These processes themselves can be regulated through phosphorylation, proteolysis, interaction with small ligands or changes in their intracellular concentration. It has been suggested that E2 can regulate the switch between early gene expression and viral genome replication during HPV infection[41]. It is possible that dimerisation of E2NT modules plays an essential role during this process. One scenario would be to activate transcription via induction of DNA loop formation at early stages of the viral life cycle. At later stages, when the concentration of expressed E2 proteins within the cell becomes high and comparable with the K_d for E2 dimer formation, free E2NT modules could compete for dimerisation with those involved in DNA loop formation and titrate them away, switching off transcription and stimulating replication. It is also possible that other protein factors could be involved in this process, including, for example, E1.

The invention therefore includes the use of E2NT crystal structure in the design of anti-viral drugs, since it is essential for viral transcription. In the rationalised computational design of drugs using the crystal structure, computational analyses are therefore necessary to determine whether a molecule or the E2NT-binding portion

thereof is sufficiently similar to the E2NT structure. Such analyses may be carried out in current software applications, such as the Molecular Similarity application of QUANTA (Molecular Simulations Inc., Waltham, Mass.) version 3.3, and as described in the accompanying User's Guide, Volume 3 pages. 134-135.

The Molecular Similarity application permits comparisons between different structures, different conformations of the same structure, and different parts of the same structure. The procedure used in Molecular Similarity to compare structures is divided into four steps: 1) load the structures to be compared; 2) define the atom equivalences in these structures; 3) perform a fitting operation; and 4) analyze the results.

Each structure is identified by a name. One structure is identified as the target (i.e., the fixed structure); all remaining structures are working structures (i.e., moving structures). Atom equivalency within QUANTA is defined by user input and, for the purpose of this invention equivalent atoms may be defined as protein backbone atoms (N, C.alpha., C and O) for all conserved residues between the two structures being compared. We will also consider only rigid fitting operations.

When a rigid fitting method is used, the working structure is translated and rotated to obtain an optimum fit with the target structure. The fitting operation uses a least squares fitting algorithm that computes the optimum translation and rotation to be applied to the moving structure, such that the root mean square difference of the fit over the specified pairs of equivalent atom is an absolute minimum. This number, given in angstroms, is reported by QUANTA.

For the purpose of one class of embodiments this invention, any set of structure coordinates of a molecule or molecular complex that has a root mean square deviation of conserved residue backbone atoms (N, C.alpha., C, O) of less than 1.5 .ANG. when superimposed--using backbone atoms--on the relevant structure coordinates of E2NT are considered identical. More preferably, the root mean square

deviation is less than 1.0 .ANG.. Most preferably, the root mean square deviation is less than 0.5 .ANG..

The term "root mean square deviation" means the square root of the arithmetic mean of the squares of the deviations from the mean. It is a way to express the deviation or variation from a trend or object. For purposes of this invention, the "root mean square deviation" defines the variation in the backbone of a protein from the backbone of E2NT a dimerising portion thereof, for example as defined by the structure coordinates of E2NT described herein.

The term "least squares" refers to a method based on the principle that the best estimate of a value is that in which the sum of the squares of the deviations of observed values is a minimum.

Materials and Methods

Purification and crystallisation.

Details of the purification and crystallisation of E2NT have been described previously[16]. Briefly, the ORF encoding the N-terminal 201 residues of HPV-16 E2 was cloned into the prokaryotic expression plasmid pET15b downstream of the 20-residue His-tag leader sequence; protein was expressed in *E. coli*BL21(DE3)pLysS and purified using nickel affinity and anion exchange chromatography. Crystals were obtained by hanging drop vapour diffusion with 0.8-1.2M ammonium sulphate, 0.1M triethanolamine pH 8.0-8.3 and 3-5% 2-methyl-2,4-pentanediol. Crystals grew only with very fresh protein preparations and deteriorated in terms of diffraction quality in less than a week. This necessitated freezing and storage of crystals in liquid nitrogen immediately after growth, as discussed above.

Structure determination.

All data were recorded on cryogenically frozen crystals. A native crystal was frozen for which initial data were recorded to 3.4 Å[16]. For the screening of derivatives,

crystal stability was even more limiting. Nine crystals were soaked in various heavy atom reagents immediately after growth. The crystals were screened in-house using a MAR research imaging plate on a Rigaku RU200 rotating anode source, by recording 3° of data for each and analysing the fractional isomorphous difference from the native. Three derivatives showed promising differences from the native, in the range of 15-20% after scaling using SCALEPACK[42] and were stored in liquid nitrogen. The native crystal was transported to EMBL Hamburg where 1.9 Å data were measured using synchrotron radiation from beam line X11, Table 1. In addition data were recorded at EMBL for the three promising derivatives to about 2.7 Å. Two of these derivatives proved useful in phase determination and the structure was solved by multiple isomorphous replacement with anomalous scattering (MIRAS) at 2.7 Å. The two derivatives were solved independently using the CCP4 suite[43]from the difference Patterson synthesis and by direct methods as implemented in SHELX[44]. Both contained a single heavy atom site. Phases, calculated using MLPHARE, were enhanced by solvent flattening4[5] using a solvent content of 50 %. The resulting high quality density map was easily interpretable and the initial model was built using QUANTA (Molecular Simulations) for all but four residues of the construct, ignoring the His-tag. The model was completed with REFMAC (resolution 20-1.9 Å) using a bulk solvent correction, to an R-factor of 23.3 % (R_{Free} 29.7 % - for 5 % of the data). There are 221 residues in the recombinant protein: the first twenty comprise the His-Tag. The final model contains all but two of the 201 residues of the real protein: residues 125-126 are disordered and lie in a flexible surface loop. Only one residue, His0, of the His-tag has clear density and an ordered conformation. In addition there are 187 water molecules, which were selected using ARP[46]during the course of refinement. The main statistics of the refined model are shown in Table 2.

Analytical ultracentrifugation.

Experiments were carried out in an Optima XL-A ultracentrifuge (Beckman-Coultier, CA, USA) using scanning UV optics. During the experiments, the recombinant E2NT was in 10mM TrisHCl pH 8.0, 5mM DTT, 0.2 mM EDTA, 300 mM NaCl.

Data were obtained at rotor speeds of 12,000 and 16,000 rpm, and the time to equilibrium was 10-12 hours. All runs were carried out at 293K, and all radial scans were at a wavelength of 280 nm. Dissociation constants were obtained by nonlinear regression using the Beckman ultracentrifuge software.

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Table 1

X-ray data and phasing statistics

Data set	Native	UAc	AuCN
Space Group	$P3_121$	$P3_121$	$P3_121$
a ,b (Å)	54.68	54.49	54.58
c (Å)	155.73	155.66	156.50
Resolution (Å)	30-1.9	20-2.7	20 - 2.7
Temperature, K	120	120	120
Wavelength (Å)	0.86	0.86	0.86
Unique reflections	21751	7873	7937
Completeness (%) (outer shell)	98.8 (89.3)	99.8 (96.1)	99.7 (93.8)
R-merge (outer shell)	0.058 (0.339)	0.073 (0.271)	0.061 (0.268)
Phasing Power: (centric / acentric)		1.55 / 2.07	0.95 / 1.40
FOM: MIRAS		0.59	
FOM: DM 20-2.7 Å (2.7 - 1.9 Å)		0.88 (0.61)	
DM: Mean phase change (20-2.7 Å)		32 °	
R-factor (FreeR)	0.223 (0.295)		

Table 2

Refinement and model correlation

Resolution			1.9 – 10.0 Å
Number of protein atoms			1622
Number of solvent sites			211
Number of reflections used in refinement			20637
Number of reflections used for Rfree calculation	1111		
R-factor ‡			0.232
Rfree ‡			0.305
Average atomic B-factor*, Å^2	protein atoms		38.0
	water molecules		48.5
R.m.s. deviations from ideal geometry (Å). Targets in parentheses			
	bond distance		0.013 (0.020)
	angle distance		0.026 (0.040)
	chiral volume		0.142 (0.200)

‡Crystallographic R-factor, $R_{(free)} = \sum ||F_o| - |F_c|| / \sum |F_o|$.

Table 3

```
CRYST    54.680   54.680  155.730  90.00  90.00 120.00 P3121
SCALE1       0.01829   0.01056   0.00000         0.00000
SCALE2       0.00000   0.02112   0.00000         0.00000
SCALE3       0.00000   0.00000   0.00642         0.00000
ATOM      1  N   HIS A   0       5.469 -26.512  52.262  1.00 61.92
ATOM      2  CA  HIS A   0       6.434 -25.669  51.568  1.00 61.84
ATOM      3  C   HIS A   0       6.263 -25.743  50.051  1.00 53.91
ATOM      4  O   HIS A   0       6.089 -24.713  49.607  1.00 69.59
ATOM      5  CB  HIS A   0       7.837 -26.127  51.965  1.00 54.18
ATOM      6  CG  HIS A   0       7.848 -26.468  53.431  0.00 99.00
ATOM      7  ND1 HIS A   0       7.914 -25.533  54.412  0.00 99.00
ATOM      8  CD2 HIS A   0       7.732 -27.728  54.027  0.00 99.00
ATOM      9  CE1 HIS A   0       7.828 -26.215  55.570  0.00 99.00
ATOM     10  NE2 HIS A   0       7.723 -27.531  55.370  0.00 99.00
ATOM     11  N   MET A   1       6.663 -26.896  49.478  1.00 56.24
ATOM     12  CA  MET A   1       6.435 -27.076  48.053  1.00 56.42
ATOM     13  C   MET A   1       5.209 -26.282  47.619  1.00 56.07
ATOM     14  O   MET A   1       5.293 -25.299  46.911  1.00 56.51
ATOM     15  CB  MET A   1       6.216 -28.565  47.788  1.00 60.46
ATOM     16  CG  MET A   1       6.856 -29.020  46.477  0.00 99.00
ATOM     17  SD  MET A   1       7.244 -30.775  46.483  0.00 99.00
ATOM     18  CE  MET A   1       7.499 -30.975  44.711  0.00 99.00
ATOM     19  N   GLU A   2       4.035 -26.755  48.064  1.00 54.92
ATOM     20  CA  GLU A   2       2.803 -26.044  47.744  1.00 53.59
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ATOM     16  CG  MET A   1       6.856 -29.020  46.477  0.00 99.00
ATOM     17  SD  MET A   1       7.244 -30.775  46.483  0.00 99.00
ATOM     18  CE  MET A   1       7.499 -30.975  44.711  0.00 99.00
ATOM     19  N   GLU A   2       4.035 -26.755  48.064  1.00 54.92
ATOM     20  CA  GLU A   2       2.803 -26.044  47.744  1.00 53.59
ATOM     21  C   GLU A   2       2.870 -24.570  48.154  1.00 52.81
ATOM     22  O   GLU A   2       2.555 -23.664  47.393  1.00 51.69
ATOM     23  CB  GLU A   2       1.661 -26.740  48.482  1.00 56.88
ATOM     24  CG  GLU A   2       2.090 -28.092  49.054  0.00 99.00
ATOM     25  CD  GLU A   2       1.019 -28.610  49.983  0.00 99.00
ATOM     26  OE1 GLU A   2       0.454 -27.819  50.722  0.00 99.00
ATOM     27  OE2 GLU A   2       0.761 -29.811  49.963  0.00 99.00
ATOM     28  N   THR A   3       3.260 -24.346  49.424  1.00 52.06
ATOM     29  CA  THR A   3       3.300 -22.980  49.940  1.00 51.61
ATOM     30  C   THR A   3       4.161 -22.059  49.070  1.00 50.30
ATOM     31  O   THR A   3       3.731 -21.006  48.617  1.00 49.91
ATOM     32  CB  THR A   3       3.858 -23.023  51.364  1.00 54.31
ATOM     33  OG1 THR A   3       2.975 -23.789  52.187  1.00 56.98
ATOM     34  CG2 THR A   3       3.960 -21.605  51.935  1.00 55.18
ATOM     35  N   LEU A   4       5.372 -22.498  48.717  1.00 50.11
ATOM     36  CA  LEU A   4       6.201 -21.696  47.808  1.00 50.48
ATOM     37  C   LEU A   4       5.553 -21.516  46.444  1.00 50.18
ATOM     38  O   LEU A   4       5.520 -20.410  45.877  1.00 50.73
ATOM     39  CB  LEU A   4       7.603 -22.286  47.626  1.00 52.72
ATOM     40  CG  LEU A   4       8.545 -22.252  48.826  1.00 56.58
ATOM     41  CD1 LEU A   4       9.819 -23.035  48.583  1.00 55.37
ATOM     42  CD2 LEU A   4       8.829 -20.828  49.288  1.00 56.27
ATOM     43  N   CYS A   5       5.028 -22.615  45.885  1.00 49.77
ATOM     44  CA  CYS A   5       4.362 -22.530  44.587  1.00 48.93
ATOM     45  C   CYS A   5       3.218 -21.534  44.589  1.00 48.27
ATOM     46  O   CYS A   5       3.136 -20.698  43.682  1.00 47.03
ATOM     47  CB  CYS A   5       3.865 -23.879  44.075  1.00 49.50
ATOM     48  SG  CYS A   5       5.217 -24.972  43.626  1.00 50.79
ATOM     49  N   GLN A   6       2.356 -21.627  45.610  1.00 46.85
ATOM     50  CA  GLN A   6       1.227 -20.718  45.675  1.00 47.22
ATOM     51  C   GLN A   6       1.666 -19.276  45.865  1.00 46.83
ATOM     52  O   GLN A   6       1.050 -18.382  45.276  1.00 48.60
ATOM     53  CB  GLN A   6       0.272 -21.079  46.817  1.00 50.54
ATOM     54  CG  GLN A   6      -0.681 -22.221  46.515  1.00 55.34
ATOM     55  CD  GLN A   6      -1.144 -22.875  47.806  1.00 59.63
ATOM     56  OE1 GLN A   6      -1.101 -22.222  48.853  1.00 61.52
ATOM     57  NE2 GLN A   6      -1.482 -24.156  47.775  1.00 57.45
ATOM     58  N   ARG A   7       2.628 -19.035  46.757  1.00 46.33
ATOM     59  CA  ARG A   7       3.162 -17.700  46.938  1.00 46.38
ATOM     60  C   ARG A   7       3.780 -17.145  45.650  1.00 44.90
ATOM     61  O   ARG A   7       3.544 -15.986  45.355  1.00 45.29
ATOM     62  CB  ARG A   7       4.267 -17.682  48.013  1.00 50.84
ATOM     63  CG  ARG A   7       3.690 -17.869  49.418  1.00 62.38
ATOM     64  CD  ARG A   7       2.884 -16.616  49.765  1.00 71.41
ATOM     65  NE  ARG A   7       3.786 -15.539  50.171  1.00 78.82
ATOM     66  CZ  ARG A   7       3.406 -14.307  50.474  1.00 83.50
ATOM     67  NH1 ARG A   7       2.122 -13.965  50.423  1.00 85.24
ATOM     68  NH2 ARG A   7       4.316 -13.410  50.841  1.00 85.59
ATOM     69  N   LEU A   8       4.608 -17.918  44.984  1.00 45.22
ATOM     70  CA  LEU A   8       5.212 -17.429  43.728  1.00 45.85
ATOM     71  C   LEU A   8       4.161 -17.110  42.672  1.00 46.67
ATOM     72  O   LEU A   8       4.197 -16.055  42.025  1.00 46.25
ATOM     73  CB  LEU A   8       6.185 -18.477  43.194  1.00 41.52
ATOM     74  CG  LEU A   8       6.979 -18.054  41.944  1.00 44.17
ATOM     75  CD1 LEU A   8       7.941 -16.924  42.283  1.00 44.96
ATOM     76  CD2 LEU A   8       7.723 -19.246  41.373  1.00 44.18
ATOM     77  N   ASN A   9       3.193 -18.014  42.508  1.00 47.73
ATOM     78  CA  ASN A   9       2.065 -17.825  41.610  1.00 48.73
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ATOM     79  C   ASN A   9       1.351 -16.516  41.925  1.00 48.98
ATOM     80  O   ASN A   9       1.136 -15.727  40.999  1.00 48.98
ATOM     81  CB  ASN A   9       1.011 -18.923  41.725  1.00 54.35
ATOM     82  CG  ASN A   9       1.220 -20.167  40.912  1.00 58.01
ATOM     83  OD1 ASN A   9       2.281 -20.427  40.356  1.00 60.06
ATOM     84  ND2 ASN A   9       0.174 -20.991  40.841  1.00 63.02
ATOM     85  N   VAL A  10       1.047 -16.267  43.206  1.00 48.31
ATOM     86  CA  VAL A  10       0.388 -15.003  43.528  1.00 48.22
ATOM     87  C   VAL A  10       1.338 -13.837  43.252  1.00 48.34
ATOM     88  O   VAL A  10       0.931 -12.816  42.688  1.00 47.81
ATOM     89  CB  VAL A  10      -0.111 -14.918  44.981  1.00 53.07
ATOM     90  CG1 VAL A  10      -0.501 -13.487  45.353  1.00 53.77
ATOM     91  CG2 VAL A  10      -1.328 -15.827  45.176  1.00 54.90
ATOM     92  N   CYS A  11       2.601 -14.011  43.661  1.00 47.68
ATOM     93  CA  CYS A  11       3.570 -12.938  43.426  1.00 47.78
ATOM     94  C   CYS A  11       3.747 -12.615  41.954  1.00 47.29
ATOM     95  O   CYS A  11       3.632 -11.473  41.499  1.00 47.31
ATOM     96  CB  CYS A  11       4.893 -13.269  44.144  1.00 48.13
ATOM     97  SG  CYS A  11       6.077 -11.884  44.082  1.00 44.06
ATOM     98  N   GLN A  12       3.903 -13.633  41.120  1.00 47.63
ATOM     99  CA  GLN A  12       4.150 -13.484  39.702  1.00 48.32
ATOM    100  C   GLN A  12       2.936 -12.946  38.951  1.00 48.82
ATOM    101  O   GLN A  12       3.103 -12.258  37.946  1.00 48.64
ATOM    102  CB  GLN A  12       4.657 -14.783  39.092  1.00 45.97
ATOM    103  CG  GLN A  12       6.018 -15.213  39.590  1.00 45.90
ATOM    104  CD  GLN A  12       6.659 -16.359  38.862  1.00 46.71
ATOM    105  OE1 GLN A  12       6.028 -17.320  38.425  1.00 45.33
ATOM    106  NE2 GLN A  12       7.983 -16.294  38.702  1.00 49.43
ATOM    107  N   ASP A  13       1.736 -13.199  39.470  1.00 48.93
ATOM    108  CA  ASP A  13       0.516 -12.691  38.853  1.00 49.49
ATOM    109  C   ASP A  13       0.413 -11.198  39.085  1.00 49.55
ATOM    110  O   ASP A  13       0.082 -10.444  38.171  1.00 49.73
ATOM    111  CB  ASP A  13      -0.732 -13.392  39.411  1.00 52.95
ATOM    112  CG  ASP A  13      -0.955 -14.680  38.932  0.00 99.00
ATOM    113  OD1 ASP A  13      -0.110 -15.160  38.175  0.00 99.00
ATOM    114  OD2 ASP A  13      -2.054 -15.191  39.132  0.00 99.00
ATOM    115  N   LYS A  14       0.801 -10.735  40.269  1.00 48.95
ATOM    116  CA  LYS A  14       0.809  -9.313  40.556  1.00 49.25
ATOM    117  C   LYS A  14       1.794  -8.575  39.658  1.00 49.07
ATOM    118  O   LYS A  14       1.470  -7.519  39.119  1.00 49.78
ATOM    119  CB  LYS A  14       1.109  -9.040  42.030  1.00 52.53
ATOM    120  CG  LYS A  14      -0.070  -8.421  42.768  1.00 62.87
ATOM    121  CD  LYS A  14      -0.269  -6.975  42.329  1.00 66.42
ATOM    122  CE  LYS A  14      -1.227  -6.247  43.257  1.00 70.58
ATOM    123  NZ  LYS A  14      -0.835  -4.824  43.452  1.00 72.01
ATOM    124  N   ILE A  15       2.984  -9.131  39.468  1.00 48.82
ATOM    125  CA  ILE A  15       3.992  -8.530  38.595  1.00 49.56
ATOM    126  C   ILE A  15       3.467  -8.390  37.165  1.00 50.17
ATOM    127  O   ILE A  15       3.538  -7.324  36.561  1.00 50.19
ATOM    128  CB  ILE A  15       5.288  -9.359  38.669  1.00 43.08
ATOM    129  CG1 ILE A  15       5.931  -9.100  40.054  1.00 45.94
ATOM    130  CG2 ILE A  15       6.286  -8.951  37.597  1.00 47.46
ATOM    131  CD1 ILE A  15       6.960 -10.120  40.472  1.00 42.94
ATOM    132  N   LEU A  16       2.880  -9.437  36.623  1.00 51.16
ATOM    133  CA  LEU A  16       2.272  -9.406  35.291  1.00 52.54
ATOM    134  C   LEU A  16       1.135  -8.414  35.191  1.00 52.81
ATOM    135  O   LEU A  16       1.023  -7.678  34.194  1.00 53.37
ATOM    136  CB  LEU A  16       1.859 -10.810  34.847  1.00 56.20
ATOM    137  CG  LEU A  16       3.067 -11.696  34.504  1.00 61.93
ATOM    138  CD1 LEU A  16       2.816 -13.139  34.904  1.00 65.17
ATOM    139  CD2 LEU A  16       3.456 -11.572  33.041  1.00 62.31
ATOM    140  N   THR A  17       0.274  -8.336  36.204  1.00 52.95
ATOM    141  CA  THR A  17      -0.789  -7.332  36.217  1.00 53.67
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ATOM    142  C   THR A  17      -0.232  -5.916  36.173  1.00 54.28
ATOM    143  O   THR A  17      -0.860  -5.026  35.590  1.00 54.21
ATOM    144  CB  THR A  17      -1.677  -7.468  37.468  1.00 55.51
ATOM    145  OG1 THR A  17      -2.321  -8.742  37.469  1.00 54.73
ATOM    146  CG2 THR A  17      -2.713  -6.355  37.551  1.00 52.35
ATOM    147  N   HIS A  18       0.879  -5.647  36.878  1.00 53.99
ATOM    148  CA  HIS A  18       1.495  -4.331  36.754  1.00 54.39
ATOM    149  C   HIS A  18       1.960  -4.115  35.313  1.00 55.01
ATOM    150  O   HIS A  18       1.722  -3.036  34.757  1.00 54.91
ATOM    151  CB  HIS A  18       2.663  -4.168  37.735  1.00 53.19
ATOM    152  CG  HIS A  18       2.198  -3.867  39.130  1.00 52.86
ATOM    153  ND1 HIS A  18       1.486  -2.733  39.432  1.00 52.60
ATOM    154  CD2 HIS A  18       2.362  -4.553  40.296  1.00 52.72
ATOM    155  CE1 HIS A  18       1.216  -2.720  40.730  1.00 53.99
ATOM    156  NE2 HIS A  18       1.735  -3.817  41.269  1.00 53.27
ATOM    157  N   TYR A  19       2.580  -5.122  34.721  1.00 56.14
ATOM    158  CA  TYR A  19       3.044  -5.034  33.337  1.00 58.17
ATOM    159  C   TYR A  19       1.890  -4.733  32.380  1.00 58.92
ATOM    160  O   TYR A  19       1.957  -3.827  31.552  1.00 59.36
ATOM    161  CB  TYR A  19       3.759  -6.320  32.950  1.00 59.47
ATOM    162  CG  TYR A  19       5.097  -6.621  33.580  1.00 62.05
ATOM    163  CD1 TYR A  19       5.983  -5.607  33.934  1.00 63.22
ATOM    164  CD2 TYR A  19       5.513  -7.934  33.787  1.00 62.96
ATOM    165  CE1 TYR A  19       7.212  -5.891  34.488  1.00 63.58
ATOM    166  CE2 TYR A  19       6.745  -8.226  34.345  1.00 63.59
ATOM    167  CZ  TYR A  19       7.597  -7.199  34.703  1.00 63.46
ATOM    168  OH  TYR A  19       8.828  -7.470  35.274  1.00 62.56
ATOM    169  N   GLU A  20       0.779  -5.451  32.499  1.00 59.63
ATOM    170  CA  GLU A  20      -0.426  -5.196  31.734  1.00 59.76
ATOM    171  C   GLU A  20      -0.990  -3.804  31.918  1.00 59.59
ATOM    172  O   GLU A  20      -1.198  -3.103  30.928  1.00 59.90
ATOM    173  CB  GLU A  20      -1.499  -6.241  32.056  1.00 66.29
ATOM    174  CG  GLU A  20      -1.176  -7.583  31.409  1.00 73.88
ATOM    175  CD  GLU A  20      -2.142  -8.678  31.815  1.00 78.60
ATOM    176  OE1 GLU A  20      -1.749  -9.862  31.692  1.00 82.52
ATOM    177  OE2 GLU A  20      -3.272  -8.365  32.242  1.00 78.94
ATOM    178  N   ASN A  21      -1.186  -3.340  33.145  1.00 59.04
ATOM    179  CA  ASN A  21      -1.784  -2.053  33.404  1.00 57.97
ATOM    180  C   ASN A  21      -1.002  -0.853  32.918  1.00 57.50
ATOM    181  O   ASN A  21      -1.637   0.118  32.496  1.00 57.19
ATOM    182  CB  ASN A  21      -2.149  -1.876  34.875  1.00 61.71
ATOM    183  CG  ASN A  21      -3.089  -2.964  35.362  1.00 63.07
ATOM    184  OD1 ASN A  21      -3.691  -3.685  34.563  1.00 60.88
ATOM    185  ND2 ASN A  21      -3.161  -3.066  36.685  1.00 62.59
ATOM    186  N   ASP A  22       0.327  -0.826  33.022  1.00 56.38
ATOM    187  CA  ASP A  22       1.080   0.299  32.480  1.00 54.54
ATOM    188  C   ASP A  22       0.710   1.630  33.112  1.00 53.00
ATOM    189  O   ASP A  22       0.632   2.652  32.424  1.00 52.65
ATOM    190  CB  ASP A  22       0.818   0.369  30.967  1.00 61.62
ATOM    191  CG  ASP A  22       2.107   0.655  30.214  1.00 65.99
ATOM    192  OD1 ASP A  22       2.946   1.402  30.765  1.00 64.95
ATOM    193  OD2 ASP A  22       2.235   0.116  29.099  1.00 69.58
ATOM    194  N   SER A  23       0.616   1.683  34.440  1.00 50.98
ATOM    195  CA  SER A  23       0.213   2.879  35.148  1.00 49.25
ATOM    196  C   SER A  23       1.294   3.960  35.095  1.00 48.02
ATOM    197  O   SER A  23       2.450   3.746  34.740  1.00 47.57
ATOM    198  CB  SER A  23      -0.101   2.633  36.640  1.00 46.04
ATOM    199  OG  SER A  23       0.549   1.424  36.984  1.00 56.16
ATOM    200  N   THR A  24       0.847   5.152  35.441  1.00 47.42
ATOM    201  CA  THR A  24       1.724   6.312  35.512  1.00 48.00
ATOM    202  C   THR A  24       1.731   6.860  36.920  1.00 47.34
ATOM    203  O   THR A  24       2.328   7.898  37.173  1.00 47.41
ATOM    204  CB  THR A  24       1.369   7.421  34.505  1.00 50.50
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ATOM    205  OG1 THR A  24       0.042   7.871  34.734  1.00 51.02
ATOM    206  CG2 THR A  24       1.558   6.901  33.094  1.00 48.60
ATOM    207  N   ASP A  25       1.124   6.096  37.828  1.00 46.98
ATOM    208  CA  ASP A  25       1.058   6.453  39.234  1.00 46.50
ATOM    209  C   ASP A  25       2.193   5.788  40.013  1.00 45.63
ATOM    210  O   ASP A  25       2.376   4.578  40.042  1.00 44.95
ATOM    211  CB  ASP A  25      -0.286   6.024  39.847  1.00 53.36
ATOM    212  CG  ASP A  25      -1.442   6.789  39.202  1.00 62.10
ATOM    213  OD1 ASP A  25      -1.605   7.997  39.498  1.00 64.72
ATOM    214  OD2 ASP A  25      -2.185   6.192  38.392  1.00 62.72
ATOM    215  N   LEU A  26       3.000   6.633  40.614  1.00 45.40
ATOM    216  CA  LEU A  26       4.167   6.207  41.381  1.00 45.37
ATOM    217  C   LEU A  26       3.834   5.157  42.418  1.00 45.85
ATOM    218  O   LEU A  26       4.563   4.170  42.565  1.00 46.38
ATOM    219  CB  LEU A  26       4.763   7.483  41.982  1.00 44.87
ATOM    220  CG  LEU A  26       6.056   7.341  42.783  1.00 44.69
ATOM    221  CD1 LEU A  26       7.128   6.688  41.931  1.00 40.20
ATOM    222  CD2 LEU A  26       6.529   8.703  43.267  1.00 46.93
ATOM    223  N   ARG A  27       2.741   5.281  43.178  1.00 45.28
ATOM    224  CA  ARG A  27       2.266   4.241  44.065  1.00 45.19
ATOM    225  C   ARG A  27       2.251   2.841  43.483  1.00 44.47
ATOM    226  O   ARG A  27       2.610   1.886  44.187  1.00 44.56
ATOM    227  CB  ARG A  27       0.852   4.494  44.607  1.00 51.04
ATOM    228  CG  ARG A  27       0.713   5.531  45.690  1.00 61.27
ATOM    229  CD  ARG A  27      -0.715   6.081  45.714  1.00 66.89
ATOM    230  NE  ARG A  27      -0.927   6.984  46.839  1.00 75.54
ATOM    231  CZ  ARG A  27      -2.083   7.555  47.170  1.00 79.36
ATOM    232  NH1 ARG A  27      -3.184   7.331  46.456  1.00 80.70
ATOM    233  NH2 ARG A  27      -2.152   8.359  48.228  1.00 79.78
ATOM    234  N   ASP A  28       1.771   2.632  42.255  1.00 43.06
ATOM    235  CA  ASP A  28       1.785   1.318  41.648  1.00 41.77
ATOM    236  C   ASP A  28       3.195   0.797  41.385  1.00 41.18
ATOM    237  O   ASP A  28       3.408  -0.409  41.402  1.00 40.08
ATOM    238  CB  ASP A  28       1.014   1.325  40.303  1.00 44.91
ATOM    239  CG  ASP A  28      -0.450   1.655  40.560  1.00 53.31
ATOM    240  OD1 ASP A  28      -1.014   2.560  39.920  1.00 53.29
ATOM    241  OD2 ASP A  28      -1.022   0.983  41.446  1.00 52.80
ATOM    242  N   HIS A  29       4.132   1.700  41.062  1.00 40.87
ATOM    243  CA  HIS A  29       5.510   1.269  40.787  1.00 40.10
ATOM    244  C   HIS A  29       6.208   0.795  42.073  1.00 39.08
ATOM    245  O   HIS A  29       6.987  -0.143  42.045  1.00 38.12
ATOM    246  CB  HIS A  29       6.246   2.473  40.166  1.00 40.60
ATOM    247  CG  HIS A  29       5.590   2.806  38.837  1.00 42.13
ATOM    248  ND1 HIS A  29       5.069   1.810  38.042  1.00 42.28
ATOM    249  CD2 HIS A  29       5.373   3.980  38.192  1.00 44.10
ATOM    250  CE1 HIS A  29       4.552   2.348  36.943  1.00 43.73
ATOM    251  NE2 HIS A  29       4.738   3.656  37.014  1.00 42.95
ATOM    252  N   ILE A  30       5.896   1.454  43.152  1.00 39.44
ATOM    253  CA  ILE A  30       6.339   0.990  44.501  1.00 39.95
ATOM    254  C   ILE A  30       5.899  -0.426  44.746  1.00 40.09
ATOM    255  O   ILE A  30       6.658  -1.303  45.181  1.00 41.16
ATOM    256  CB  ILE A  30       5.843   1.991  45.550  1.00 40.65
ATOM    257  CG1 ILE A  30       6.563   3.321  45.334  1.00 40.86
ATOM    258  CG2 ILE A  30       6.125   1.537  47.004  1.00 41.39
ATOM    259  CD1 ILE A  30       6.060   4.498  46.138  1.00 42.24
ATOM    260  N   ASP A  31       4.631  -0.764  44.485  1.00 41.09
ATOM    261  CA  ASP A  31       4.082  -2.089  44.758  1.00 40.37
ATOM    262  C   ASP A  31       4.718  -3.130  43.856  1.00 40.59
ATOM    263  O   ASP A  31       4.965  -4.277  44.244  1.00 40.70
ATOM    264  CB  ASP A  31       2.566  -2.080  44.459  1.00 42.53
ATOM    265  CG  ASP A  31       1.886  -3.379  44.801  1.00 44.66
ATOM    266  OD1 ASP A  31       1.799  -4.311  43.991  1.00 46.03
ATOM    267  OD2 ASP A  31       1.495  -3.517  45.987  1.00 53.28
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ATOM    268  N   TYR A  32       4.945  -2.735  42.589  1.00 39.00
ATOM    269  CA  TYR A  32       5.636  -3.647  41.677  1.00 38.51
ATOM    270  C   TYR A  32       7.017  -4.030  42.231  1.00 36.55
ATOM    271  O   TYR A  32       7.359  -5.204  42.252  1.00 36.44
ATOM    272  CB  TYR A  32       5.765  -2.921  40.324  1.00 39.37
ATOM    273  CG  TYR A  32       6.750  -3.532  39.369  1.00 42.61
ATOM    274  CD1 TYR A  32       6.374  -4.668  38.646  1.00 45.04
ATOM    275  CD2 TYR A  32       8.005  -2.989  39.141  1.00 43.12
ATOM    276  CE1 TYR A  32       7.245  -5.272  37.758  1.00 46.06
ATOM    277  CE2 TYR A  32       8.871  -3.576  38.235  1.00 44.10
ATOM    278  CZ  TYR A  32       8.489  -4.707  37.545  1.00 45.75
ATOM    279  OH  TYR A  32       9.322  -5.303  36.633  1.00 44.58
ATOM    280  N   TRP A  33       7.850  -3.064  42.552  1.00 36.14
ATOM    281  CA  TRP A  33       9.183  -3.384  43.061  1.00 36.59
ATOM    282  C   TRP A  33       9.144  -4.146  44.391  1.00 36.80
ATOM    283  O   TRP A  33      10.050  -4.951  44.634  1.00 37.42
ATOM    284  CB  TRP A  33      10.054  -2.131  43.159  1.00 37.44
ATOM    285  CG  TRP A  33      10.588  -1.813  41.780  1.00 34.77
ATOM    286  CD1 TRP A  33      10.244  -0.745  40.979  1.00 35.47
ATOM    287  CD2 TRP A  33      11.522  -2.605  41.047  1.00 32.86
ATOM    288  NE1 TRP A  33      10.974  -0.822  39.805  1.00 32.84
ATOM    289  CE2 TRP A  33      11.735  -1.947  39.799  1.00 35.43
ATOM    290  CE3 TRP A  33      12.209  -3.792  41.301  1.00 32.38
ATOM    291  CZ2 TRP A  33      12.595  -2.444  38.832  1.00 35.55
ATOM    292  CZ3 TRP A  33      13.061  -4.282  40.337  1.00 37.27
ATOM    293  CH2 TRP A  33      13.245  -3.626  39.108  1.00 38.28
ATOM    294  N   LYS A  34       8.150  -3.912  45.246  1.00 37.05
ATOM    295  CA  LYS A  34       7.990  -4.765  46.437  1.00 37.56
ATOM    296  C   LYS A  34       7.687  -6.205  46.060  1.00 37.90
ATOM    297  O   LYS A  34       8.220  -7.124  46.684  1.00 37.29
ATOM    298  CB  LYS A  34       6.860  -4.261  47.345  1.00 36.29
ATOM    299  CG  LYS A  34       7.111  -2.871  47.891  1.00 41.05
ATOM    300  CD  LYS A  34       6.095  -2.498  48.945  1.00 47.20
ATOM    301  CE  LYS A  34       5.764  -1.032  48.964  1.00 49.66
ATOM    302  NZ  LYS A  34       5.046  -0.625  50.219  1.00 57.26
ATOM    303  N   HIS A  35       6.853  -6.411  45.025  1.00 37.50
ATOM    304  CA  HIS A  35       6.670  -7.779  44.525  1.00 36.43
ATOM    305  C   HIS A  35       7.913  -8.328  43.875  1.00 35.96
ATOM    306  O   HIS A  35       8.237  -9.523  43.986  1.00 34.61
ATOM    307  CB  HIS A  35       5.446  -7.901  43.587  1.00 40.23
ATOM    308  CG  HIS A  35       4.200  -7.883  44.428  1.00 44.09
ATOM    309  ND1 HIS A  35       3.567  -6.711  44.788  1.00 48.39
ATOM    310  CD2 HIS A  35       3.539  -8.879  45.058  1.00 48.71
ATOM    311  CE1 HIS A  35       2.538  -6.985  45.574  1.00 48.93
ATOM    312  NE2 HIS A  35       2.524  -8.283  45.774  1.00 47.98
ATOM    313  N   MET A  36       8.665  -7.457  43.180  1.00 35.13
ATOM    314  CA  MET A  36       9.927  -7.985  42.606  1.00 35.12
ATOM    315  C   MET A  36      10.836  -8.474  43.753  1.00 35.05
ATOM    316  O   MET A  36      11.472  -9.504  43.634  1.00 34.78
ATOM    317  CB  MET A  36      10.584  -6.890  41.772  1.00 36.78
ATOM    318  CG  MET A  36       9.832  -6.601  40.454  1.00 38.38
ATOM    319  SD  MET A  36      10.026  -7.870  39.206  1.00 39.79
ATOM    320  CE  MET A  36      11.681  -7.505  38.605  1.00 43.43
ATOM    321  N   ARG A  37      10.903  -7.746  44.853  1.00 35.39
ATOM    322  CA  ARG A  37      11.729  -8.145  46.004  1.00 35.09
ATOM    323  C   ARG A  37      11.240  -9.438  46.667  1.00 34.61
ATOM    324  O   ARG A  37      12.028 -10.319  46.996  1.00 33.53
ATOM    325  CB  ARG A  37      11.555  -7.001  47.018  1.00 34.72
ATOM    326  CG  ARG A  37      12.370  -7.186  48.305  1.00 34.13
ATOM    327  CD  ARG A  37      12.132  -5.981  49.197  1.00 34.07
ATOM    328  NE  ARG A  37      12.665  -6.189  50.551  1.00 35.48
ATOM    329  CZ  ARG A  37      12.420  -5.313  51.520  1.00 33.64
ATOM    330  NH1 ARG A  37      11.676  -4.228  51.375  1.00 38.49
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ATOM    331  NH2 ARG A  37      12.948  -5.572  52.719  1.00 32.86
ATOM    332  N   LEU A  38       9.920  -9.544  46.841  1.00 33.92
ATOM    333  CA  LEU A  38       9.330 -10.768  47.372  1.00 34.82
ATOM    334  C   LEU A  38       9.592 -11.985  46.532  1.00 36.08
ATOM    335  O   LEU A  38       9.879 -13.050  47.066  1.00 35.88
ATOM    336  CB  LEU A  38       7.806 -10.549  47.542  1.00 37.00
ATOM    337  CG  LEU A  38       7.048 -11.843  47.862  1.00 39.41
ATOM    338  CD1 LEU A  38       7.338 -12.303  49.271  1.00 36.17
ATOM    339  CD2 LEU A  38       5.544 -11.698  47.633  1.00 42.91
ATOM    340  N   GLU A  39       9.532 -11.873  45.176  1.00 36.01
ATOM    341  CA  GLU A  39       9.903 -12.982  44.328  1.00 35.41
ATOM    342  C   GLU A  39      11.310 -13.492  44.650  1.00 35.95
ATOM    343  O   GLU A  39      11.524 -14.706  44.610  1.00 34.71
ATOM    344  CB  GLU A  39       9.826 -12.621  42.814  1.00 33.83
ATOM    345  CG  GLU A  39       9.999 -13.858  41.944  1.00 35.55
ATOM    346  CD  GLU A  39      10.153 -13.499  40.467  1.00 44.56
ATOM    347  OE1 GLU A  39      11.229 -12.997  40.106  1.00 42.84
ATOM    348  OE2 GLU A  39       9.219 -13.700  39.690  1.00 42.80
ATOM    349  N   CYS A  40      12.280 -12.600  44.916  1.00 35.37
ATOM    350  CA  CYS A  40      13.616 -13.054  45.262  1.00 35.02
ATOM    351  C   CYS A  40      13.603 -13.852  46.574  1.00 35.78
ATOM    352  O   CYS A  40      14.329 -14.842  46.621  1.00 35.14
ATOM    353  CB  CYS A  40      14.587 -11.879  45.434  1.00 34.19
ATOM    354  SG  CYS A  40      14.743 -10.845  43.945  1.00 35.07
ATOM    355  N   ALA A  41      12.796 -13.419  47.540  1.00 36.59
ATOM    356  CA  ALA A  41      12.772 -14.160  48.820  1.00 38.13
ATOM    357  C   ALA A  41      12.191 -15.553  48.590  1.00 37.52
ATOM    358  O   ALA A  41      12.659 -16.527  49.200  1.00 38.32
ATOM    359  CB  ALA A  41      11.955 -13.380  49.827  1.00 36.08
ATOM    360  N   ILE A  42      11.221 -15.674  47.663  1.00 37.54
ATOM    361  CA  ILE A  42      10.629 -16.995  47.397  1.00 36.18
ATOM    362  C   ILE A  42      11.626 -17.922  46.753  1.00 36.44
ATOM    363  O   ILE A  42      11.856 -19.069  47.133  1.00 35.31
ATOM    364  CB  ILE A  42       9.325 -16.907  46.581  1.00 36.30
ATOM    365  CG1 ILE A  42       8.225 -16.165  47.345  1.00 38.51
ATOM    366  CG2 ILE A  42       8.865 -18.282  46.108  1.00 38.23
ATOM    367  CD1 ILE A  42       7.114 -15.700  46.390  1.00 41.57
ATOM    368  N   TYR A  43      12.321 -17.436  45.707  1.00 35.53
ATOM    369  CA  TYR A  43      13.341 -18.254  45.060  1.00 36.20
ATOM    370  C   TYR A  43      14.479 -18.536  46.047  1.00 36.21
ATOM    371  O   TYR A  43      15.091 -19.597  45.993  1.00 36.69
ATOM    372  CB  TYR A  43      13.884 -17.474  43.838  1.00 36.61
ATOM    373  CG  TYR A  43      13.065 -17.637  42.572  1.00 38.55
ATOM    374  CD1 TYR A  43      12.717 -16.512  41.820  1.00 39.59
ATOM    375  CD2 TYR A  43      12.644 -18.871  42.116  1.00 39.53
ATOM    376  CE1 TYR A  43      11.998 -16.626  40.646  1.00 41.22
ATOM    377  CE2 TYR A  43      11.943 -19.006  40.918  1.00 40.40
ATOM    378  CZ  TYR A  43      11.604 -17.884  40.210  1.00 40.78
ATOM    379  OH  TYR A  43      10.847 -17.954  39.081  1.00 41.19
ATOM    380  N   TYR A  44      14.794 -17.563  46.906  1.00 35.43
ATOM    381  CA  TYR A  44      15.933 -17.815  47.811  1.00 37.45
ATOM    382  C   TYR A  44      15.547 -19.008  48.716  1.00 37.65
ATOM    383  O   TYR A  44      16.329 -19.945  48.876  1.00 38.00
ATOM    384  CB  TYR A  44      16.205 -16.555  48.635  1.00 38.20
ATOM    385  CG  TYR A  44      17.445 -16.670  49.503  1.00 40.09
ATOM    386  CD1 TYR A  44      17.398 -17.286  50.756  1.00 41.30
ATOM    387  CD2 TYR A  44      18.663 -16.206  49.041  1.00 40.77
ATOM    388  CE1 TYR A  44      18.569 -17.412  51.492  1.00 42.23
ATOM    389  CE2 TYR A  44      19.833 -16.312  49.776  1.00 42.80
ATOM    390  CZ  TYR A  44      19.746 -16.907  51.023  1.00 43.39
ATOM    391  OH  TYR A  44      20.863 -17.049  51.798  1.00 45.51
ATOM    392  N   LYS A  45      14.334 -18.982  49.224  1.00 38.11
ATOM    393  CA  LYS A  45      13.891 -20.078  50.118  1.00 40.98
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ATOM    394  C   LYS A  45      13.832 -21.403  49.387  1.00 41.49
ATOM    395  O   LYS A  45      14.315 -22.472  49.789  1.00 42.02
ATOM    396  CB  LYS A  45      12.537 -19.754  50.750  1.00 40.25
ATOM    397  CG  LYS A  45      11.968 -20.894  51.614  1.00 48.19
ATOM    398  CD  LYS A  45      12.824 -21.269  52.813  1.00 51.93
ATOM    399  CE  LYS A  45      12.671 -20.308  53.983  1.00 59.68
ATOM    400  NZ  LYS A  45      13.979 -20.145  54.698  1.00 61.34
ATOM    401  N   ALA A  46      13.307 -21.357  48.139  1.00 42.39
ATOM    402  CA  ALA A  46      13.230 -22.586  47.356  1.00 41.88
ATOM    403  C   ALA A  46      14.613 -23.167  47.179  1.00 41.96
ATOM    404  O   ALA A  46      14.828 -24.368  47.347  1.00 42.06
ATOM    405  CB  ALA A  46      12.561 -22.294  46.004  1.00 45.41
ATOM    406  N   ARG A  47      15.605 -22.341  46.839  1.00 42.18
ATOM    407  CA  ARG A  47      16.967 -22.806  46.649  1.00 42.89
ATOM    408  C   ARG A  47      17.567 -23.364  47.949  1.00 44.97
ATOM    409  O   ARG A  47      18.270 -24.377  47.899  1.00 44.85
ATOM    410  CB  ARG A  47      17.873 -21.700  46.134  1.00 39.95
ATOM    411  CG  ARG A  47      19.278 -22.115  45.751  1.00 44.08
ATOM    412  CD  ARG A  47      19.323 -23.087  44.564  1.00 51.87
ATOM    413  NE  ARG A  47      20.701 -23.450  44.306  1.00 57.92
ATOM    414  CZ  ARG A  47      21.372 -24.042  43.351  1.00 62.27
ATOM    415  NH1 ARG A  47      20.819 -24.506  42.243  1.00 60.85
ATOM    416  NH2 ARG A  47      22.696 -24.175  43.516  1.00 66.76
ATOM    417  N   GLU A  48      17.287 -22.673  49.051  1.00 45.14
ATOM    418  CA  GLU A  48      17.783 -23.090  50.364  1.00 48.18
ATOM    419  C   GLU A  48      17.266 -24.500  50.681  1.00 48.66
ATOM    420  O   GLU A  48      18.009 -25.362  51.122  1.00 49.01
ATOM    421  CB  GLU A  48      17.202 -22.208  51.472  1.00 50.97
ATOM    422  CG  GLU A  48      17.987 -21.039  51.955  1.00 59.37
ATOM    423  CD  GLU A  48      17.911 -20.689  53.432  1.00 58.91
ATOM    424  OE1 GLU A  48      16.891 -20.144  53.912  1.00 64.65
ATOM    425  OE2 GLU A  48      18.904 -20.949  54.156  1.00 64.43
ATOM    426  N   MET A  49      16.000 -24.730  50.361  1.00 49.75
ATOM    427  CA  MET A  49      15.358 -26.017  50.510  1.00 50.42
ATOM    428  C   MET A  49      15.738 -27.106  49.543  1.00 50.69
ATOM    429  O   MET A  49      15.197 -28.218  49.620  1.00 51.52
ATOM    430  CB  MET A  49      13.840 -25.835  50.513  1.00 53.09
ATOM    431  CG  MET A  49      13.351 -25.048  51.719  1.00 55.67
ATOM    432  SD  MET A  49      11.617 -24.613  51.508  1.00 64.13
ATOM    433  CE  MET A  49      10.922 -24.927  53.123  1.00 64.34
ATOM    434  N   GLY A  50      16.616 -26.852  48.592  1.00 50.09
ATOM    435  CA  GLY A  50      17.159 -27.787  47.664  1.00 48.51
ATOM    436  C   GLY A  50      16.332 -27.949  46.384  1.00 48.34
ATOM    437  O   GLY A  50      16.603 -28.920  45.679  1.00 47.16
ATOM    438  N   PHE A  51      15.383 -27.074  46.084  1.00 48.32
ATOM    439  CA  PHE A  51      14.628 -27.205  44.837  1.00 48.99
ATOM    440  C   PHE A  51      15.442 -26.616  43.675  1.00 49.10
ATOM    441  O   PHE A  51      16.187 -25.659  43.884  1.00 48.66
ATOM    442  CB  PHE A  51      13.266 -26.527  44.904  1.00 54.66
ATOM    443  CG  PHE A  51      12.370 -27.030  46.005  1.00 62.30
ATOM    444  CD1 PHE A  51      12.237 -28.382  46.261  1.00 66.64
ATOM    445  CD2 PHE A  51      11.648 -26.142  46.784  1.00 64.64
ATOM    446  CE1 PHE A  51      11.418 -28.837  47.281  1.00 67.20
ATOM    447  CE2 PHE A  51      10.813 -26.584  47.788  1.00 65.80
ATOM    448  CZ  PHE A  51      10.708 -27.937  48.047  1.00 65.88
ATOM    449  N   LYS A  52      15.455 -27.331  42.554  1.00 49.49
ATOM    450  CA  LYS A  52      16.204 -26.877  41.377  1.00 48.93
ATOM    451  C   LYS A  52      15.254 -26.192  40.393  1.00 47.94
ATOM    452  O   LYS A  52      15.644 -25.414  39.516  1.00 46.65
ATOM    453  CB  LYS A  52      16.905 -28.073  40.739  1.00 54.00
ATOM    454  CG  LYS A  52      17.964 -28.697  41.640  1.00 61.04
ATOM    455  CD  LYS A  52      18.931 -29.536  40.811  1.00 64.27
ATOM    456  CE  LYS A  52      19.717 -30.537  41.711  0.00 99.00
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ATOM    457  NZ  LYS A  52      20.300 -31.674  41.001  0.00 99.00
ATOM    458  N   HIS A  53      13.968 -26.480  40.589  1.00 46.17
ATOM    459  CA  HIS A  53      12.924 -25.816  39.834  1.00 45.58
ATOM    460  C   HIS A  53      11.697 -25.685  40.724  1.00 44.64
ATOM    461  O   HIS A  53      11.566 -26.465  41.649  1.00 44.95
ATOM    462  CB  HIS A  53      12.568 -26.542  38.531  1.00 44.28
ATOM    463  CG  HIS A  53      11.635 -27.700  38.758  1.00 46.45
ATOM    464  ND1 HIS A  53      10.277 -27.525  38.978  1.00 45.21
ATOM    465  CD2 HIS A  53      11.868 -29.026  38.829  1.00 45.27
ATOM    466  CE1 HIS A  53       9.709 -28.698  39.163  1.00 45.18
ATOM    467  NE2 HIS A  53      10.655 -29.629  39.076  1.00 49.44
ATOM    468  N   ILE A  54      10.895 -24.693  40.468  1.00 43.90
ATOM    469  CA  ILE A  54       9.598 -24.513  41.100  1.00 44.62
ATOM    470  C   ILE A  54       8.589 -24.354  39.976  1.00 43.53
ATOM    471  O   ILE A  54       8.704 -23.454  39.123  1.00 44.50
ATOM    472  CB  ILE A  54       9.627 -23.258  41.996  1.00 51.01
ATOM    473  CG1 ILE A  54       8.222 -22.740  42.337  1.00 51.18
ATOM    474  CG2 ILE A  54      10.420 -22.138  41.313  1.00 54.51
ATOM    475  CD1 ILE A  54       8.293 -22.022  43.690  1.00 55.08
ATOM    476  N   ASN A  55       7.679 -25.327  39.853  1.00 42.57
ATOM    477  CA  ASN A  55       6.719 -25.332  38.748  1.00 41.98
ATOM    478  C   ASN A  55       7.391 -25.383  37.389  1.00 41.70
ATOM    479  O   ASN A  55       6.958 -24.848  36.368  1.00 41.10
ATOM    480  CB  ASN A  55       5.639 -24.266  38.828  1.00 41.18
ATOM    481  CG  ASN A  55       4.611 -24.596  39.915  1.00 45.37
ATOM    482  OD1 ASN A  55       4.481 -25.766  40.285  1.00 42.95
ATOM    483  ND2 ASN A  55       3.908 -23.589  40.393  1.00 49.59
ATOM    484  N   HIS A  56       8.508 -26.115  37.343  1.00 42.09
ATOM    485  CA  HIS A  56       9.304 -26.336  36.155  1.00 41.80
ATOM    486  C   HIS A  56       9.996 -25.085  35.651  1.00 42.37
ATOM    487  O   HIS A  56      10.579 -25.115  34.573  1.00 41.39
ATOM    488  CB  HIS A  56       8.509 -27.081  35.059  1.00 38.13
ATOM    489  CG  HIS A  56       8.140 -28.417  35.639  1.00 39.93
ATOM    490  ND1 HIS A  56       8.997 -29.476  35.683  1.00 40.64
ATOM    491  CD2 HIS A  56       7.000 -28.811  36.253  1.00 40.69
ATOM    492  CE1 HIS A  56       8.401 -30.496  36.292  1.00 46.16
ATOM    493  NE2 HIS A  56       7.192 -30.108  36.648  1.00 44.07
ATOM    494  N   GLN A  57      10.115 -24.074  36.492  1.00 42.01
ATOM    495  CA  GLN A  57      10.867 -22.845  36.209  1.00 43.31
ATOM    496  C   GLN A  57      12.178 -22.922  37.011  1.00 42.73
ATOM    497  O   GLN A  57      12.135 -23.367  38.159  1.00 42.65
ATOM    498  CB  GLN A  57      10.017 -21.730  36.771  1.00 44.03
ATOM    499  CG  GLN A  57      10.191 -20.286  36.476  1.00 54.62
ATOM    500  CD  GLN A  57       8.889 -19.530  36.723  1.00 54.38
ATOM    501  OE1 GLN A  57       8.881 -18.332  36.990  1.00 54.35
ATOM    502  NE2 GLN A  57       7.774 -20.248  36.641  1.00 57.38
ATOM    503  N   VAL A  58      13.308 -22.526  36.435  1.00 41.67
ATOM    504  CA  VAL A  58      14.592 -22.695  37.122  1.00 41.06
ATOM    505  C   VAL A  58      14.654 -21.870  38.395  1.00 39.90
ATOM    506  O   VAL A  58      14.141 -20.751  38.425  1.00 40.26
ATOM    507  CB  VAL A  58      15.766 -22.343  36.168  1.00 41.94
ATOM    508  CG1 VAL A  58      15.770 -20.860  35.859  1.00 41.59
ATOM    509  CG2 VAL A  58      17.085 -22.872  36.676  1.00 43.75
ATOM    510  N   VAL A  59      15.193 -22.451  39.461  1.00 40.08
ATOM    511  CA  VAL A  59      15.414 -21.673  40.713  1.00 40.24
ATOM    512  C   VAL A  59      16.878 -21.205  40.635  1.00 39.98
ATOM    513  O   VAL A  59      17.761 -22.042  40.559  1.00 41.27
ATOM    514  CB  VAL A  59      15.250 -22.591  41.945  1.00 40.48
ATOM    515  CG1 VAL A  59      15.437 -21.777  43.243  1.00 44.12
ATOM    516  CG2 VAL A  59      13.830 -23.161  42.037  1.00 39.62
ATOM    517  N   PRO A  60      17.121 -19.911  40.686  1.00 40.13
ATOM    518  CA  PRO A  60      18.466 -19.380  40.576  1.00 40.49
ATOM    519  C   PRO A  60      19.312 -19.737  41.806  1.00 40.57
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ATOM	520	O	PRO	A	60	18.766	-20.039	42.863	1.00	39.38
ATOM	521	CB	PRO	A	60	18.272	-17.874	40.580	1.00	40.12
ATOM	522	CG	PRO	A	60	16.837	-17.576	40.657	1.00	40.26
ATOM	523	CD	PRO	A	60	16.069	-18.866	40.722	1.00	39.33
ATOM	524	N	THR	A	61	20.627	-19.662	41.632	1.00	39.59
ATOM	525	CA	THR	A	61	21.502	-19.731	42.799	1.00	39.51
ATOM	526	C	THR	A	61	21.145	-18.651	43.803	1.00	38.37
ATOM	527	O	THR	A	61	20.503	-17.621	43.545	1.00	37.40
ATOM	528	CB	THR	A	61	23.000	-19.670	42.486	1.00	42.80
ATOM	529	OG1	THR	A	61	23.259	-18.498	41.695	1.00	42.80
ATOM	530	CG2	THR	A	61	23.435	-20.914	41.722	1.00	42.91
ATOM	531	N	LEU	A	62	21.544	-18.931	45.058	1.00	37.77
ATOM	532	CA	LEU	A	62	21.280	-17.966	46.132	1.00	36.91
ATOM	533	C	LEU	A	62	21.841	-16.582	45.847	1.00	36.03
ATOM	534	O	LEU	A	62	21.248	-15.566	46.209	1.00	36.36
ATOM	535	CB	LEU	A	62	21.904	-18.492	47.447	1.00	35.93
ATOM	536	CG	LEU	A	62	21.278	-19.807	47.950	1.00	36.47
ATOM	537	CD1	LEU	A	62	22.090	-20.339	49.139	1.00	44.24
ATOM	538	CD2	LEU	A	62	19.850	-19.557	48.450	1.00	33.58
ATOM	539	N	ALA	A	63	23.053	-16.511	45.336	1.00	36.59
ATOM	540	CA	ALA	A	63	23.729	-15.236	45.091	1.00	36.90
ATOM	541	C	ALA	A	63	22.946	-14.476	44.014	1.00	36.28
ATOM	542	O	ALA	A	63	22.808	-13.263	44.128	1.00	35.61
ATOM	543	CB	ALA	A	63	25.153	-15.402	44.601	1.00	39.35
ATOM	544	N	VAL	A	64	22.430	-15.198	43.013	1.00	35.11
ATOM	545	CA	VAL	A	64	21.587	-14.456	42.054	1.00	35.89
ATOM	546	C	VAL	A	64	20.370	-13.842	42.720	1.00	35.12
ATOM	547	O	VAL	A	64	20.062	-12.664	42.487	1.00	34.59
ATOM	548	CB	VAL	A	64	21.180	-15.331	40.855	1.00	37.44
ATOM	549	CG1	VAL	A	64	20.071	-14.660	40.053	1.00	40.96
ATOM	550	CG2	VAL	A	64	22.390	-15.680	40.014	1.00	36.95
ATOM	551	N	SER	A	65	19.616	-14.592	43.540	1.00	35.09
ATOM	552	CA	SER	A	65	18.477	-14.039	44.238	1.00	34.42
ATOM	553	C	SER	A	65	18.854	-12.961	45.225	1.00	34.48
ATOM	554	O	SER	A	65	18.110	-11.986	45.326	1.00	34.19
ATOM	555	CB	SER	A	65	17.583	-15.074	44.940	1.00	34.49
ATOM	556	OG	SER	A	65	17.165	-16.015	43.951	1.00	35.80
ATOM	557	N	LYS	A	66	19.977	-13.079	45.922	1.00	34.79
ATOM	558	CA	LYS	A	66	20.365	-11.976	46.828	1.00	35.44
ATOM	559	C	LYS	A	66	20.611	-10.670	46.044	1.00	35.50
ATOM	560	O	LYS	A	66	20.219	-9.590	46.478	1.00	35.28
ATOM	561	CB	LYS	A	66	21.709	-12.362	47.478	1.00	36.28
ATOM	562	CG	LYS	A	66	21.492	-13.207	48.738	1.00	43.87
ATOM	563	CD	LYS	A	66	22.772	-13.202	49.570	1.00	52.29
ATOM	564	CE	LYS	A	66	23.722	-14.338	49.256	1.00	56.53
ATOM	565	NZ	LYS	A	66	24.326	-14.857	50.541	1.00	60.41
ATOM	566	N	ASN	A	67	21.345	-10.788	44.956	1.00	35.53
ATOM	567	CA	ASN	A	67	21.679	-9.615	44.136	1.00	35.43
ATOM	568	C	ASN	A	67	20.452	-8.955	43.544	1.00	34.46
ATOM	569	O	ASN	A	67	20.370	-7.741	43.518	1.00	33.85
ATOM	570	CB	ASN	A	67	22.657	-10.003	43.019	1.00	39.24
ATOM	571	CG	ASN	A	67	22.999	-8.797	42.163	1.00	49.34
ATOM	572	OD1	ASN	A	67	22.646	-8.711	40.977	1.00	55.32
ATOM	573	ND2	ASN	A	67	23.611	-7.794	42.784	1.00	51.11
ATOM	574	N	LYS	A	68	19.505	-9.746	43.007	1.00	34.69
ATOM	575	CA	LYS	A	68	18.245	-9.160	42.532	1.00	33.90
ATOM	576	C	LYS	A	68	17.421	-8.525	43.620	1.00	33.51
ATOM	577	O	LYS	A	68	16.726	-7.530	43.412	1.00	32.16
ATOM	578	CB	LYS	A	68	17.439	-10.259	41.811	1.00	35.44
ATOM	579	CG	LYS	A	68	18.132	-10.664	40.503	1.00	38.74
ATOM	580	CD	LYS	A	68	17.352	-11.710	39.729	1.00	44.24
ATOM	581	CE	LYS	A	68	15.976	-11.178	39.345	1.00	46.97
ATOM	582	NZ	LYS	A	68	15.414	-12.058	38.260	1.00	51.68

ATOM	583	N	ALA	A	69	17.395	-9.098	44.856	1.00	33.48
ATOM	584	CA	ALA	A	69	16.654	-8.440	45.924	1.00	33.17
ATOM	585	C	ALA	A	69	17.299	-7.103	46.282	1.00	31.99
ATOM	586	O	ALA	A	69	16.620	-6.105	46.498	1.00	31.80
ATOM	587	CB	ALA	A	69	16.642	-9.315	47.213	1.00	31.02
ATOM	588	N	LEU	A	70	18.627	-7.019	46.312	1.00	32.54
ATOM	589	CA	LEU	A	70	19.278	-5.715	46.511	1.00	32.22
ATOM	590	C	LEU	A	70	18.830	-4.668	45.471	1.00	32.04
ATOM	591	O	LEU	A	70	18.604	-3.504	45.815	1.00	32.18
ATOM	592	CB	LEU	A	70	20.800	-5.876	46.425	1.00	35.34
ATOM	593	CG	LEU	A	70	21.431	-6.582	47.652	1.00	41.35
ATOM	594	CD1	LEU	A	70	22.952	-6.614	47.488	1.00	47.21
ATOM	595	CD2	LEU	A	70	21.124	-5.797	48.927	1.00	42.20
ATOM	596	N	GLN	A	71	18.732	-5.068	44.222	1.00	32.28
ATOM	597	CA	GLN	A	71	18.336	-4.184	43.118	1.00	32.66
ATOM	598	C	GLN	A	71	16.888	-3.744	43.319	1.00	33.12
ATOM	599	O	GLN	A	71	16.599	-2.548	43.262	1.00	34.13
ATOM	600	CB	GLN	A	71	18.506	-4.847	41.767	1.00	32.48
ATOM	601	CG	GLN	A	71	19.933	-5.100	41.321	1.00	36.30
ATOM	602	CD	GLN	A	71	20.143	-5.912	40.083	1.00	36.39
ATOM	603	OE1	GLN	A	71	21.103	-5.642	39.339	1.00	42.50
ATOM	604	NE2	GLN	A	71	19.349	-6.917	39.755	1.00	33.68
ATOM	605	N	ALA	A	72	16.008	-4.697	43.668	1.00	32.97
ATOM	606	CA	ALA	A	72	14.624	-4.358	43.963	1.00	32.73
ATOM	607	C	ALA	A	72	14.529	-3.414	45.129	1.00	33.36
ATOM	608	O	ALA	A	72	13.741	-2.468	45.153	1.00	33.02
ATOM	609	CB	ALA	A	72	13.751	-5.597	44.164	1.00	31.63
ATOM	610	N	ILE	A	73	15.314	-3.700	46.205	1.00	32.96
ATOM	611	CA	ILE	A	73	15.341	-2.754	47.321	1.00	32.98
ATOM	612	C	ILE	A	73	15.756	-1.358	46.932	1.00	33.05
ATOM	613	O	ILE	A	73	15.173	-0.371	47.407	1.00	31.52
ATOM	614	CB	ILE	A	73	16.262	-3.309	48.450	1.00	32.37
ATOM	615	CG1	ILE	A	73	15.549	-4.497	49.099	1.00	34.48
ATOM	616	CG2	ILE	A	73	16.564	-2.217	49.479	1.00	36.05
ATOM	617	CD1	ILE	A	73	16.442	-5.452	49.895	1.00	36.56
ATOM	618	N	GLU	A	74	16.821	-1.221	46.107	1.00	33.20
ATOM	619	CA	GLU	A	74	17.249	0.135	45.770	1.00	34.02
ATOM	620	C	GLU	A	74	16.127	0.888	45.042	1.00	33.88
ATOM	621	O	GLU	A	74	15.924	2.077	45.333	1.00	33.58
ATOM	622	CB	GLU	A	74	18.483	0.128	44.849	1.00	42.88
ATOM	623	CG	GLU	A	74	19.730	-0.391	45.551	1.00	50.60
ATOM	624	CD	GLU	A	74	20.121	0.534	46.697	1.00	55.46
ATOM	625	OE1	GLU	A	74	19.809	0.219	47.869	1.00	54.43
ATOM	626	OE2	GLU	A	74	20.627	1.630	46.386	1.00	51.96
ATOM	627	N	LEU	A	75	15.444	0.203	44.142	1.00	34.25
ATOM	628	CA	LEU	A	75	14.353	0.814	43.393	1.00	34.85
ATOM	629	C	LEU	A	75	13.181	1.091	44.339	1.00	35.22
ATOM	630	O	LEU	A	75	12.683	2.215	44.292	1.00	35.32
ATOM	631	CB	LEU	A	75	13.895	-0.038	42.211	1.00	33.68
ATOM	632	CG	LEU	A	75	14.632	0.175	40.849	1.00	40.28
ATOM	633	CD1	LEU	A	75	14.246	1.524	40.263	1.00	38.74
ATOM	634	CD2	LEU	A	75	16.134	0.148	41.044	1.00	41.33
ATOM	635	N	GLN	A	76	12.769	0.098	45.129	1.00	35.20
ATOM	636	CA	GLN	A	76	11.711	0.401	46.107	1.00	34.63
ATOM	637	C	GLN	A	76	12.023	1.622	46.951	1.00	34.20
ATOM	638	O	GLN	A	76	11.197	2.539	47.032	1.00	33.10
ATOM	639	CB	GLN	A	76	11.439	-0.800	47.043	1.00	37.30
ATOM	640	CG	GLN	A	76	10.346	-0.570	48.086	1.00	36.76
ATOM	641	CD	GLN	A	76	10.511	-1.541	49.275	1.00	38.06
ATOM	642	OE1	GLN	A	76	11.019	-2.647	49.179	1.00	36.12
ATOM	643	NE2	GLN	A	76	10.136	-1.178	50.481	1.00	39.68
ATOM	644	N	LEU	A	77	13.195	1.702	47.596	1.00	34.42
ATOM	645	CA	LEU	A	77	13.533	2.857	48.402	1.00	34.29

ATOM	646	C	LEU	A	77	13.506	4.183	47.638	1.00	34.87
ATOM	647	O	LEU	A	77	13.070	5.221	48.149	1.00	32.77
ATOM	648	CB	LEU	A	77	14.906	2.756	49.079	1.00	31.33
ATOM	649	CG	LEU	A	77	14.976	1.566	50.093	1.00	33.32
ATOM	650	CD1	LEU	A	77	16.417	1.466	50.566	1.00	35.24
ATOM	651	CD2	LEU	A	77	14.094	1.902	51.303	1.00	32.76
ATOM	652	N	THR	A	78	14.094	4.162	46.440	1.00	35.43
ATOM	653	CA	THR	A	78	14.147	5.391	45.644	1.00	35.16
ATOM	654	C	THR	A	78	12.754	5.938	45.407	1.00	34.62
ATOM	655	O	THR	A	78	12.561	7.128	45.655	1.00	35.48
ATOM	656	CB	THR	A	78	14.869	5.117	44.306	1.00	33.75
ATOM	657	OG1	THR	A	78	16.212	4.853	44.644	1.00	36.55
ATOM	658	CG2	THR	A	78	14.710	6.309	43.359	1.00	35.96
ATOM	659	N	LEU	A	79	11.867	5.059	44.971	1.00	35.23
ATOM	660	CA	LEU	A	79	10.492	5.458	44.646	1.00	35.59
ATOM	661	C	LEU	A	79	9.738	5.941	45.879	1.00	36.24
ATOM	662	O	LEU	A	79	8.923	6.848	45.814	1.00	34.44
ATOM	663	CB	LEU	A	79	9.744	4.326	43.961	1.00	37.56
ATOM	664	CG	LEU	A	79	10.302	3.825	42.611	1.00	40.81
ATOM	665	CD1	LEU	A	79	9.415	2.708	42.066	1.00	36.86
ATOM	666	CD2	LEU	A	79	10.404	4.981	41.632	1.00	44.33
ATOM	667	N	GLU	A	80	10.058	5.284	47.023	1.00	35.96
ATOM	668	CA	GLU	A	80	9.487	5.773	48.285	1.00	35.25
ATOM	669	C	GLU	A	80	10.002	7.132	48.672	1.00	35.81
ATOM	670	O	GLU	A	80	9.241	7.941	49.182	1.00	36.57
ATOM	671	CB	GLU	A	80	9.805	4.764	49.414	1.00	33.47
ATOM	672	CG	GLU	A	80	8.923	3.555	49.368	1.00	36.03
ATOM	673	CD	GLU	A	80	9.390	2.431	50.293	1.00	39.80
ATOM	674	OE1	GLU	A	80	10.528	2.453	50.789	1.00	38.34
ATOM	675	OE2	GLU	A	80	8.587	1.482	50.397	1.00	40.54
ATOM	676	N	THR	A	81	11.266	7.474	48.443	1.00	35.85
ATOM	677	CA	THR	A	81	11.759	8.819	48.714	1.00	37.65
ATOM	678	C	THR	A	81	11.074	9.798	47.742	1.00	39.27
ATOM	679	O	THR	A	81	10.711	10.894	48.159	1.00	38.93
ATOM	680	CB	THR	A	81	13.277	8.895	48.523	1.00	38.88
ATOM	681	OG1	THR	A	81	13.854	8.188	49.626	1.00	41.45
ATOM	682	CG2	THR	A	81	13.827	10.315	48.511	1.00	37.76
ATOM	683	N	ILE	A	82	10.887	9.360	46.500	1.00	39.69
ATOM	684	CA	ILE	A	82	10.176	10.260	45.568	1.00	41.32
ATOM	685	C	ILE	A	82	8.727	10.458	45.979	1.00	42.17
ATOM	686	O	ILE	A	82	8.195	11.566	45.910	1.00	42.11
ATOM	687	CB	ILE	A	82	10.199	9.735	44.134	1.00	38.27
ATOM	688	CG1	ILE	A	82	11.619	9.500	43.651	1.00	39.22
ATOM	689	CG2	ILE	A	82	9.462	10.697	43.194	1.00	37.66
ATOM	690	CD1	ILE	A	82	12.489	10.717	43.731	1.00	43.59
ATOM	691	N	TYR	A	83	8.097	9.376	46.426	1.00	43.95
ATOM	692	CA	TYR	A	83	6.726	9.469	46.924	1.00	45.07
ATOM	693	C	TYR	A	83	6.597	10.496	48.038	1.00	45.84
ATOM	694	O	TYR	A	83	5.613	11.234	48.097	1.00	44.82
ATOM	695	CB	TYR	A	83	6.229	8.097	47.364	1.00	47.55
ATOM	696	CG	TYR	A	83	4.745	8.146	47.683	1.00	52.04
ATOM	697	CD1	TYR	A	83	3.826	8.070	46.643	1.00	53.71
ATOM	698	CD2	TYR	A	83	4.292	8.292	48.987	1.00	53.75
ATOM	699	CE1	TYR	A	83	2.469	8.119	46.899	1.00	55.59
ATOM	700	CE2	TYR	A	83	2.932	8.343	49.245	1.00	55.42
ATOM	701	CZ	TYR	A	83	2.036	8.252	48.199	1.00	56.63
ATOM	702	OH	TYR	A	83	0.691	8.313	48.454	1.00	58.49
ATOM	703	N	ASN	A	84	7.594	10.600	48.932	1.00	45.54
ATOM	704	CA	ASN	A	84	7.519	11.621	49.959	1.00	46.22
ATOM	705	C	ASN	A	84	7.965	12.989	49.446	1.00	45.99
ATOM	706	O	ASN	A	84	7.812	13.930	50.226	1.00	46.80
ATOM	707	CB	ASN	A	84	8.199	11.252	51.257	1.00	45.97
ATOM	708	CG	ASN	A	84	7.995	9.970	52.011	1.00	42.27

ATOM	709	OD1	ASN	A	84	6.960	9.292	51.955	1.00	48.67
ATOM	710	ND2	ASN	A	84	9.032	9.528	52.753	1.00	40.72
ATOM	711	N	SER	A	85	8.351	13.244	48.201	1.00	44.95
ATOM	712	CA	SER	A	85	8.830	14.568	47.823	1.00	43.57
ATOM	713	C	SER	A	85	7.800	15.337	46.988	1.00	43.08
ATOM	714	O	SER	A	85	6.747	14.845	46.627	1.00	41.05
ATOM	715	CB	SER	A	85	10.108	14.456	46.969	1.00	43.41
ATOM	716	OG	SER	A	85	9.782	14.024	45.656	1.00	38.06
ATOM	717	N	GLN	A	86	8.199	16.543	46.586	1.00	43.58
ATOM	718	CA	GLN	A	86	7.377	17.394	45.725	1.00	44.93
ATOM	719	C	GLN	A	86	7.185	16.853	44.331	1.00	45.37
ATOM	720	O	GLN	A	86	6.311	17.326	43.581	1.00	45.62
ATOM	721	CB	GLN	A	86	8.100	18.761	45.588	1.00	52.00
ATOM	722	CG	GLN	A	86	9.448	18.557	44.909	1.00	58.47
ATOM	723	CD	GLN	A	86	10.263	19.798	44.692	1.00	64.18
ATOM	724	OE1	GLN	A	86	11.330	19.934	45.303	1.00	70.12
ATOM	725	NE2	GLN	A	86	9.786	20.668	43.810	1.00	65.51
ATOM	726	N	TYR	A	87	8.002	15.875	43.915	1.00	45.13
ATOM	727	CA	TYR	A	87	7.886	15.277	42.601	1.00	44.09
ATOM	728	C	TYR	A	87	6.898	14.125	42.585	1.00	44.50
ATOM	729	O	TYR	A	87	6.682	13.536	41.536	1.00	43.83
ATOM	730	CB	TYR	A	87	9.231	14.748	42.072	1.00	42.80
ATOM	731	CG	TYR	A	87	10.318	15.782	42.226	1.00	41.15
ATOM	732	CD1	TYR	A	87	11.376	15.539	43.084	1.00	41.11
ATOM	733	CD2	TYR	A	87	10.272	17.010	41.567	1.00	39.57
ATOM	734	CE1	TYR	A	87	12.344	16.496	43.319	1.00	41.24
ATOM	735	CE2	TYR	A	87	11.243	17.967	41.779	1.00	39.89
ATOM	736	CZ	TYR	A	87	12.295	17.693	42.614	1.00	40.85
ATOM	737	OH	TYR	A	87	13.302	18.594	42.842	1.00	41.44
ATOM	738	N	SER	A	88	6.318	13.805	43.743	1.00	45.60
ATOM	739	CA	SER	A	88	5.478	12.626	43.844	1.00	46.49
ATOM	740	C	SER	A	88	4.368	12.534	42.814	1.00	47.16
ATOM	741	O	SER	A	88	4.080	11.467	42.270	1.00	46.71
ATOM	742	CB	SER	A	88	4.816	12.633	45.245	1.00	48.13
ATOM	743	OG	SER	A	88	4.092	11.417	45.346	1.00	51.98
ATOM	744	N	ASN	A	89	3.667	13.642	42.565	1.00	48.16
ATOM	745	CA	ASN	A	89	2.563	13.593	41.604	1.00	49.94
ATOM	746	C	ASN	A	89	2.888	13.746	40.138	1.00	50.05
ATOM	747	O	ASN	A	89	1.922	13.898	39.362	1.00	49.81
ATOM	748	CB	ASN	A	89	1.500	14.616	42.040	1.00	57.17
ATOM	749	CG	ASN	A	89	1.003	14.286	43.439	1.00	62.53
ATOM	750	OD1	ASN	A	89	0.752	15.195	44.234	1.00	67.35
ATOM	751	ND2	ASN	A	89	0.884	12.995	43.737	1.00	64.39
ATOM	752	N	GLU	A	90	4.149	13.696	39.690	1.00	49.64
ATOM	753	CA	GLU	A	90	4.384	13.669	38.238	1.00	49.09
ATOM	754	C	GLU	A	90	3.952	12.346	37.610	1.00	48.60
ATOM	755	O	GLU	A	90	3.715	11.386	38.327	1.00	47.76
ATOM	756	CB	GLU	A	90	5.891	13.782	37.891	1.00	47.16
ATOM	757	CG	GLU	A	90	6.546	14.906	38.632	1.00	42.61
ATOM	758	CD	GLU	A	90	7.981	15.219	38.359	1.00	44.84
ATOM	759	OE1	GLU	A	90	8.767	14.356	37.961	1.00	46.86
ATOM	760	OE2	GLU	A	90	8.343	16.400	38.592	1.00	45.57
ATOM	761	N	LYS	A	91	3.961	12.276	36.269	1.00	47.66
ATOM	762	CA	LYS	A	91	3.798	10.985	35.595	1.00	47.27
ATOM	763	C	LYS	A	91	5.099	10.180	35.749	1.00	46.58
ATOM	764	O	LYS	A	91	6.181	10.745	35.610	1.00	45.68
ATOM	765	CB	LYS	A	91	3.615	11.124	34.076	1.00	48.52
ATOM	766	CG	LYS	A	91	2.234	10.887	33.509	1.00	55.86
ATOM	767	CD	LYS	A	91	2.206	11.249	32.017	1.00	56.83
ATOM	768	CE	LYS	A	91	2.934	10.173	31.214	1.00	56.89
ATOM	769	NZ	LYS	A	91	3.771	10.752	30.132	1.00	54.96
ATOM	770	N	TRP	A	92	4.971	8.888	36.019	1.00	46.05
ATOM	771	CA	TRP	A	92	6.082	7.961	36.101	1.00	45.89

ATOM	772	C	TRP	A	92	5.702	6.699	35.343	1.00	46.10
ATOM	773	O	TRP	A	92	4.701	6.079	35.668	1.00	46.31
ATOM	774	CB	TRP	A	92	6.454	7.556	37.550	1.00	42.18
ATOM	775	CG	TRP	A	92	6.876	8.733	38.372	1.00	37.28
ATOM	776	CD1	TRP	A	92	6.025	9.494	39.126	1.00	35.98
ATOM	777	CD2	TRP	A	92	8.170	9.326	38.526	1.00	35.45
ATOM	778	NE1	TRP	A	92	6.703	10.512	39.704	1.00	37.68
ATOM	779	CE2	TRP	A	92	8.031	10.426	39.359	1.00	34.31
ATOM	780	CE3	TRP	A	92	9.436	9.034	38.009	1.00	35.29
ATOM	781	CZ2	TRP	A	92	9.085	11.251	39.784	1.00	37.71
ATOM	782	CZ3	TRP	A	92	10.489	9.844	38.391	1.00	34.81
ATOM	783	CH2	TRP	A	92	10.320	10.920	39.272	1.00	37.49
ATOM	784	N	THR	A	93	6.468	6.302	34.333	1.00	46.29
ATOM	785	CA	THR	A	93	6.122	5.105	33.583	1.00	47.56
ATOM	786	C	THR	A	93	6.901	3.910	34.110	1.00	48.41
ATOM	787	O	THR	A	93	7.846	4.126	34.862	1.00	48.37
ATOM	788	CB	THR	A	93	6.370	5.242	32.077	1.00	46.70
ATOM	789	OG1	THR	A	93	7.740	4.928	31.792	1.00	44.41
ATOM	790	CG2	THR	A	93	6.037	6.666	31.629	1.00	44.27
ATOM	791	N	LEU	A	94	6.507	2.716	33.705	1.00	48.40
ATOM	792	CA	LEU	A	94	7.213	1.494	34.076	1.00	48.72
ATOM	793	C	LEU	A	94	8.647	1.507	33.559	1.00	48.08
ATOM	794	O	LEU	A	94	9.587	1.053	34.225	1.00	47.67
ATOM	795	CB	LEU	A	94	6.462	0.294	33.479	1.00	56.38
ATOM	796	CG	LEU	A	94	6.488	-1.036	34.232	1.00	61.49
ATOM	797	CD1	LEU	A	94	6.452	-0.872	35.741	1.00	61.80
ATOM	798	CD2	LEU	A	94	5.310	-1.900	33.781	1.00	62.20
ATOM	799	N	GLN	A	95	8.818	2.022	32.332	1.00	45.95
ATOM	800	CA	GLN	A	95	10.175	2.149	31.805	1.00	43.86
ATOM	801	C	GLN	A	95	10.956	3.201	32.555	1.00	41.09
ATOM	802	O	GLN	A	95	12.138	2.966	32.803	1.00	42.10
ATOM	803	CB	GLN	A	95	10.226	2.431	30.291	1.00	47.51
ATOM	804	CG	GLN	A	95	10.933	1.311	29.532	1.00	55.82
ATOM	805	CD	GLN	A	95	12.441	1.369	29.531	1.00	58.57
ATOM	806	OE1	GLN	A	95	13.085	2.191	28.850	1.00	63.35
ATOM	807	NE2	GLN	A	95	13.089	0.470	30.270	1.00	53.71
ATOM	808	N	ASP	A	96	10.358	4.296	32.984	1.00	39.88
ATOM	809	CA	ASP	A	96	11.048	5.272	33.814	1.00	39.85
ATOM	810	C	ASP	A	96	11.651	4.615	35.076	1.00	40.22
ATOM	811	O	ASP	A	96	12.731	5.042	35.499	1.00	39.43
ATOM	812	CB	ASP	A	96	10.115	6.397	34.246	1.00	40.26
ATOM	813	CG	ASP	A	96	9.603	7.287	33.110	1.00	43.09
ATOM	814	OD1	ASP	A	96	10.290	7.391	32.079	1.00	38.82
ATOM	815	OD2	ASP	A	96	8.516	7.883	33.274	1.00	41.58
ATOM	816	N	VAL	A	97	10.956	3.643	35.651	1.00	39.44
ATOM	817	CA	VAL	A	97	11.371	3.024	36.913	1.00	38.84
ATOM	818	C	VAL	A	97	11.979	1.641	36.744	1.00	38.61
ATOM	819	O	VAL	A	97	12.059	0.843	37.707	1.00	38.87
ATOM	820	CB	VAL	A	97	10.186	2.955	37.903	1.00	40.58
ATOM	821	CG1	VAL	A	97	9.561	4.325	38.123	1.00	37.24
ATOM	822	CG2	VAL	A	97	9.122	1.929	37.569	1.00	39.40
ATOM	823	N	SER	A	98	12.431	1.314	35.539	1.00	37.55
ATOM	824	CA	SER	A	98	12.956	0.014	35.183	1.00	36.27
ATOM	825	C	SER	A	98	14.408	-0.046	35.652	1.00	36.46
ATOM	826	O	SER	A	98	15.028	1.015	35.744	1.00	36.95
ATOM	827	CB	SER	A	98	12.915	-0.142	33.637	1.00	41.66
ATOM	828	OG	SER	A	98	13.869	0.716	32.996	1.00	41.12
ATOM	829	N	LEU	A	99	14.941	-1.247	35.831	1.00	36.38
ATOM	830	CA	LEU	A	99	16.345	-1.378	36.203	1.00	36.81
ATOM	831	C	LEU	A	99	17.251	-0.939	35.042	1.00	36.83
ATOM	832	O	LEU	A	99	18.297	-0.341	35.258	1.00	36.14
ATOM	833	CB	LEU	A	99	16.636	-2.829	36.589	1.00	42.12
ATOM	834	CG	LEU	A	99	18.056	-3.111	37.080	1.00	45.46

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ATOM    835  CD1 LEU A  99      18.330  -2.481  38.442  1.00 43.84
ATOM    836  CD2 LEU A  99      18.341  -4.606  37.072  1.00 45.55
ATOM    837  N   GLU A 100      16.797  -1.199  33.818  1.00 36.41
ATOM    838  CA  GLU A 100      17.488  -0.765  32.611  1.00 37.21
ATOM    839  C   GLU A 100      17.790   0.722  32.622  1.00 36.02
ATOM    840  O   GLU A 100      18.972   1.068  32.470  1.00 37.81
ATOM    841  CB  GLU A 100      16.690  -1.126  31.340  1.00 40.11
ATOM    842  CG  GLU A 100      17.528  -0.836  30.096  1.00 49.41
ATOM    843  CD  GLU A 100      16.866  -1.247  28.790  1.00 56.89
ATOM    844  OE1 GLU A 100      15.724  -1.755  28.761  1.00 57.99
ATOM    845  OE2 GLU A 100      17.534  -1.025  27.753  1.00 62.25
ATOM    846  N   VAL A 101      16.808   1.580  32.792  1.00 35.41
ATOM    847  CA  VAL A 101      17.044   3.010  32.973  1.00 34.54
ATOM    848  C   VAL A 101      17.897   3.329  34.185  1.00 34.62
ATOM    849  O   VAL A 101      18.899   4.082  34.151  1.00 33.43
ATOM    850  CB  VAL A 101      15.666   3.714  33.047  1.00 36.71
ATOM    851  CG1 VAL A 101      15.797   5.167  33.459  1.00 34.93
ATOM    852  CG2 VAL A 101      15.013   3.600  31.651  1.00 37.61
ATOM    853  N   TYR A 102      17.555   2.678  35.314  1.00 33.28
ATOM    854  CA  TYR A 102      18.202   3.008  36.583  1.00 33.58
ATOM    855  C   TYR A 102      19.711   2.817  36.484  1.00 33.46
ATOM    856  O   TYR A 102      20.424   3.624  37.071  1.00 33.95
ATOM    857  CB  TYR A 102      17.653   2.091  37.691  1.00 34.23
ATOM    858  CG  TYR A 102      17.996   2.494  39.103  1.00 36.50
ATOM    859  CD1 TYR A 102      17.325   3.559  39.676  1.00 36.36
ATOM    860  CD2 TYR A 102      18.961   1.811  39.855  1.00 36.63
ATOM    861  CE1 TYR A 102      17.582   3.949  40.979  1.00 37.25
ATOM    862  CE2 TYR A 102      19.237   2.202  41.162  1.00 37.64
ATOM    863  CZ  TYR A 102      18.537   3.253  41.707  1.00 36.95
ATOM    864  OH  TYR A 102      18.795   3.693  42.966  1.00 36.81
ATOM    865  N   LEU A 103      20.170   1.800  35.766  1.00 32.90
ATOM    866  CA  LEU A 103      21.575   1.513  35.625  1.00 34.69
ATOM    867  C   LEU A 103      22.225   2.188  34.422  1.00 35.97
ATOM    868  O   LEU A 103      23.434   2.037  34.247  1.00 37.11
ATOM    869  CB  LEU A 103      21.811   0.003  35.568  1.00 34.47
ATOM    870  CG  LEU A 103      21.363  -0.757  36.853  1.00 39.98
ATOM    871  CD1 LEU A 103      21.588  -2.261  36.702  1.00 40.37
ATOM    872  CD2 LEU A 103      22.104  -0.231  38.073  1.00 40.86
ATOM    873  N   THR A 104      21.460   2.913  33.614  1.00 35.72
ATOM    874  CA  THR A 104      22.115   3.606  32.468  1.00 34.87
ATOM    875  C   THR A 104      22.792   4.825  33.060  1.00 35.15
ATOM    876  O   THR A 104      22.206   5.345  34.004  1.00 35.03
ATOM    877  CB  THR A 104      21.074   4.013  31.409  1.00 36.04
ATOM    878  OG1 THR A 104      20.507   2.790  30.928  1.00 34.78
ATOM    879  CG2 THR A 104      21.709   4.722  30.211  1.00 36.74
ATOM    880  N   ALA A 105      23.907   5.292  32.541  1.00 35.32
ATOM    881  CA  ALA A 105      24.595   6.446  33.150  1.00 36.34
ATOM    882  C   ALA A 105      23.662   7.647  33.117  1.00 36.12
ATOM    883  O   ALA A 105      23.031   7.852  32.074  1.00 35.49
ATOM    884  CB  ALA A 105      25.840   6.710  32.281  1.00 36.09
ATOM    885  N   PRO A 106      23.556   8.404  34.195  1.00 35.90
ATOM    886  CA  PRO A 106      24.273   8.154  35.428  1.00 36.06
ATOM    887  C   PRO A 106      23.617   7.057  36.275  1.00 35.41
ATOM    888  O   PRO A 106      22.426   7.141  36.602  1.00 34.13
ATOM    889  CB  PRO A 106      24.167   9.484  36.175  1.00 36.61
ATOM    890  CG  PRO A 106      22.880  10.077  35.695  1.00 36.41
ATOM    891  CD  PRO A 106      22.862   9.725  34.223  1.00 36.94
ATOM    892  N   THR A 107      24.407   6.045  36.646  1.00 35.50
ATOM    893  CA  THR A 107      23.833   4.857  37.287  1.00 34.62
ATOM    894  C   THR A 107      23.256   5.142  38.651  1.00 34.93
ATOM    895  O   THR A 107      23.639   6.108  39.324  1.00 34.98
ATOM    896  CB  THR A 107      24.820   3.666  37.301  1.00 39.51
ATOM    897  OG1 THR A 107      24.114   2.516  37.812  1.00 36.86
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ATOM	898	CG2	THR	A	107	26.016	3.957	38.203	1.00	39.22
ATOM	899	N	GLY	A	108	22.272	4.352	39.091	1.00	35.80
ATOM	900	CA	GLY	A	108	21.709	4.504	40.436	1.00	35.25
ATOM	901	C	GLY	A	108	20.719	5.660	40.527	1.00	35.77
ATOM	902	O	GLY	A	108	20.469	6.140	41.646	1.00	35.22
ATOM	903	N	CYS	A	109	20.099	6.080	39.427	1.00	34.86
ATOM	904	CA	CYS	A	109	19.226	7.257	39.416	1.00	35.48
ATOM	905	C	CYS	A	109	17.997	6.934	38.551	1.00	35.39
ATOM	906	O	CYS	A	109	18.179	6.397	37.449	1.00	36.31
ATOM	907	CB	CYS	A	109	19.987	8.395	38.610	1.00	35.03
ATOM	908	SG	CYS	A	109	21.181	9.249	39.651	1.00	42.26
ATOM	909	N	ILE	A	110	16.785	7.158	39.035	1.00	34.76
ATOM	910	CA	ILE	A	110	15.613	7.181	38.156	1.00	34.74
ATOM	911	C	ILE	A	110	15.774	8.456	37.264	1.00	34.48
ATOM	912	O	ILE	A	110	16.234	9.494	37.723	1.00	32.60
ATOM	913	CB	ILE	A	110	14.315	7.414	38.954	1.00	37.69
ATOM	914	CG1	ILE	A	110	14.117	6.274	39.951	1.00	41.68
ATOM	915	CG2	ILE	A	110	13.100	7.594	38.049	1.00	39.85
ATOM	916	CD1	ILE	A	110	13.770	4.943	39.384	1.00	43.84
ATOM	917	N	LYS	A	111	15.373	8.287	36.013	1.00	34.15
ATOM	918	CA	LYS	A	111	15.522	9.400	35.086	1.00	35.30
ATOM	919	C	LYS	A	111	14.453	9.355	34.002	1.00	35.93
ATOM	920	O	LYS	A	111	13.942	8.285	33.702	1.00	35.35
ATOM	921	CB	LYS	A	111	16.879	9.488	34.449	1.00	39.11
ATOM	922	CG	LYS	A	111	17.713	8.300	34.171	1.00	44.79
ATOM	923	CD	LYS	A	111	19.195	8.574	34.494	1.00	41.27
ATOM	924	CE	LYS	A	111	19.930	7.270	34.207	1.00	41.21
ATOM	925	NZ	LYS	A	111	19.943	6.341	35.377	1.00	36.81
ATOM	926	N	LYS	A	112	14.181	10.569	33.482	1.00	36.64
ATOM	927	CA	LYS	A	112	13.194	10.511	32.410	1.00	37.12
ATOM	928	C	LYS	A	112	13.553	11.477	31.283	1.00	38.56
ATOM	929	O	LYS	A	112	14.382	12.368	31.442	1.00	37.40
ATOM	930	CB	LYS	A	112	11.784	10.464	32.883	1.00	45.17
ATOM	931	CG	LYS	A	112	11.274	11.108	34.092	1.00	43.77
ATOM	932	CD	LYS	A	112	9.855	10.826	34.592	1.00	42.31
ATOM	933	CE	LYS	A	112	9.625	11.830	35.702	1.00	40.92
ATOM	934	NZ	LYS	A	112	8.251	12.207	36.085	1.00	41.42
ATOM	935	N	HIS	A	113	12.734	11.353	30.256	1.00	38.75
ATOM	936	CA	HIS	A	113	12.848	12.198	29.053	1.00	39.66
ATOM	937	C	HIS	A	113	14.221	12.110	28.430	1.00	39.88
ATOM	938	O	HIS	A	113	14.895	13.102	28.197	1.00	40.77
ATOM	939	CB	HIS	A	113	12.341	13.611	29.366	1.00	38.57
ATOM	940	CG	HIS	A	113	11.036	13.636	30.115	1.00	38.81
ATOM	941	ND1	HIS	A	113	9.924	12.958	29.655	1.00	42.21
ATOM	942	CD2	HIS	A	113	10.680	14.172	31.299	1.00	41.13
ATOM	943	CE1	HIS	A	113	8.934	13.113	30.518	1.00	37.50
ATOM	944	NE2	HIS	A	113	9.378	13.838	31.529	1.00	43.65
ATOM	945	N	GLY	A	114	14.678	10.906	28.098	1.00	40.03
ATOM	946	CA	GLY	A	114	15.948	10.634	27.465	1.00	42.07
ATOM	947	C	GLY	A	114	15.982	10.869	25.944	1.00	42.05
ATOM	948	O	GLY	A	114	15.006	10.756	25.196	1.00	43.10
ATOM	949	N	TYR	A	115	17.172	11.210	25.445	1.00	42.78
ATOM	950	CA	TYR	A	115	17.369	11.441	24.019	1.00	42.59
ATOM	951	C	TYR	A	115	18.822	11.155	23.637	1.00	42.83
ATOM	952	O	TYR	A	115	19.673	11.182	24.526	1.00	40.37
ATOM	953	CB	TYR	A	115	17.029	12.863	23.612	1.00	43.99
ATOM	954	CG	TYR	A	115	17.877	13.912	24.298	1.00	45.80
ATOM	955	CD1	TYR	A	115	18.944	14.514	23.648	1.00	47.34
ATOM	956	CD2	TYR	A	115	17.628	14.263	25.614	1.00	47.05
ATOM	957	CE1	TYR	A	115	19.718	15.463	24.291	1.00	47.70
ATOM	958	CE2	TYR	A	115	18.375	15.230	26.260	1.00	47.78
ATOM	959	CZ	TYR	A	115	19.398	15.845	25.579	1.00	48.85
ATOM	960	OH	TYR	A	115	20.194	16.754	26.228	1.00	49.73

ATOM	961	N	THR	A	116	19.071	10.953	22.342	1.00 41.33
ATOM	962	CA	THR	A	116	20.415	10.564	21.938	1.00 42.28
ATOM	963	C	THR	A	116	21.285	11.789	21.697	1.00 42.08
ATOM	964	O	THR	A	116	20.858	12.791	21.136	1.00 42.54
ATOM	965	CB	THR	A	116	20.365	9.722	20.643	1.00 46.87
ATOM	966	OG1	THR	A	116	19.589	8.542	20.949	1.00 49.86
ATOM	967	CG2	THR	A	116	21.753	9.272	20.209	1.00 46.71
ATOM	968	N	VAL	A	117	22.552	11.650	22.045	1.00 40.95
ATOM	969	CA	VAL	A	117	23.575	12.638	21.686	1.00 40.83
ATOM	970	C	VAL	A	117	24.538	11.818	20.830	1.00 41.40
ATOM	971	O	VAL	A	117	24.850	10.689	21.222	1.00 41.22
ATOM	972	CB	VAL	A	117	24.297	13.196	22.928	1.00 39.95
ATOM	973	CG1	VAL	A	117	25.599	13.915	22.569	1.00 41.09
ATOM	974	CG2	VAL	A	117	23.375	14.216	23.617	1.00 38.93
ATOM	975	N	GLU	A	118	24.986	12.396	19.713	1.00 41.76
ATOM	976	CA	GLU	A	118	25.908	11.573	18.905	1.00 42.29
ATOM	977	C	GLU	A	118	27.254	12.265	18.832	1.00 42.60
ATOM	978	O	GLU	A	118	27.288	13.498	18.801	1.00 42.94
ATOM	979	CB	GLU	A	118	25.266	11.262	17.556	1.00 46.34
ATOM	980	CG	GLU	A	118	25.923	11.896	16.365	1.00 53.27
ATOM	981	CD	GLU	A	118	25.542	11.270	15.029	1.00 55.37
ATOM	982	OE1	GLU	A	118	24.442	10.707	14.879	1.00 54.40
ATOM	983	OE2	GLU	A	118	26.425	11.358	14.155	1.00 57.58
ATOM	984	N	VAL	A	119	28.322	11.485	18.947	1.00 41.77
ATOM	985	CA	VAL	A	119	29.661	12.031	18.909	1.00 42.33
ATOM	986	C	VAL	A	119	30.408	11.363	17.735	1.00 43.93
ATOM	987	O	VAL	A	119	30.499	10.136	17.672	1.00 42.59
ATOM	988	CB	VAL	A	119	30.486	11.790	20.187	1.00 42.91
ATOM	989	CG1	VAL	A	119	31.894	12.330	19.963	1.00 40.51
ATOM	990	CG2	VAL	A	119	29.868	12.517	21.398	1.00 38.33
ATOM	991	N	GLN	A	120	30.927	12.212	16.870	1.00 44.65
ATOM	992	CA	GLN	A	120	31.698	11.727	15.723	1.00 47.49
ATOM	993	C	GLN	A	120	33.182	11.912	16.001	1.00 50.11
ATOM	994	O	GLN	A	120	33.676	13.040	16.117	1.00 48.28
ATOM	995	CB	GLN	A	120	31.330	12.541	14.481	1.00 48.85
ATOM	996	CG	GLN	A	120	29.834	12.547	14.248	1.00 52.37
ATOM	997	CD	GLN	A	120	29.456	13.089	12.884	1.00 55.34
ATOM	998	OE1	GLN	A	120	30.319	13.536	12.135	1.00 59.08
ATOM	999	NE2	GLN	A	120	28.164	13.016	12.580	1.00 56.41
ATOM	1000	N	PHE	A	121	33.872	10.771	16.065	1.00 52.87
ATOM	1001	CA	PHE	A	121	35.287	10.824	16.382	1.00 58.51
ATOM	1002	C	PHE	A	121	36.147	11.092	15.162	1.00 62.63
ATOM	1003	O	PHE	A	121	37.367	11.134	15.318	1.00 63.15
ATOM	1004	CB	PHE	A	121	35.764	9.660	17.219	1.00 54.96
ATOM	1005	CG	PHE	A	121	35.110	9.596	18.571	1.00 55.06
ATOM	1006	CD1	PHE	A	121	33.983	8.822	18.763	1.00 54.70
ATOM	1007	CD2	PHE	A	121	35.627	10.295	19.641	1.00 52.63
ATOM	1008	CE1	PHE	A	121	33.389	8.726	20.000	1.00 54.52
ATOM	1009	CE2	PHE	A	121	35.032	10.209	20.885	1.00 53.27
ATOM	1010	CZ	PHE	A	121	33.908	9.438	21.065	1.00 53.03
ATOM	1011	N	ASP	A	122	35.547	11.249	13.988	1.00 66.78
ATOM	1012	CA	ASP	A	122	36.246	11.801	12.847	1.00 72.12
ATOM	1013	C	ASP	A	122	35.414	12.152	11.632	1.00 74.59
ATOM	1014	O	ASP	A	122	35.591	13.228	11.042	1.00 75.06
ATOM	1015	CB	ASP	A	122	37.480	10.970	12.495	1.00 80.67
ATOM	1016	CG	ASP	A	122	38.640	11.910	12.201	1.00 84.98
ATOM	1017	OD1	ASP	A	122	38.366	13.018	11.687	1.00 87.13
ATOM	1018	OD2	ASP	A	122	39.782	11.512	12.508	1.00 89.25
ATOM	1019	N	GLY	A	123	34.511	11.277	11.204	1.00 77.06
ATOM	1020	CA	GLY	A	123	33.653	11.544	10.050	1.00 79.12
ATOM	1021	C	GLY	A	123	32.499	10.546	9.975	1.00 80.59
ATOM	1022	O	GLY	A	123	32.702	9.332	10.039	1.00 80.64
ATOM	1023	N	ASP	A	124	31.278	11.063	9.813	1.00 81.67

ATOM	1024	CA	ASP	A	124	30.122	10.180	9.717	1.00	82.77
ATOM	1025	C	ASP	A	124	30.000	9.574	8.324	1.00	82.74
ATOM	1026	O	ASP	A	124	29.673	9.777	7.400	0.00	99.00
ATOM	1027	CB	ASP	A	124	28.828	10.863	10.141	1.00	87.39
ATOM	1028	CG	ASP	A	124	27.968	9.968	11.019	1.00	91.94
ATOM	1029	OD1	ASP	A	124	28.495	8.933	11.489	1.00	93.18
ATOM	1030	OD2	ASP	A	124	26.779	10.288	11.244	1.00	93.68
ATOM	1031	N	ASN	A	127	34.160	6.401	13.268	1.00	58.22
ATOM	1032	CA	ASN	A	127	33.743	5.964	14.601	1.00	58.81
ATOM	1033	C	ASN	A	127	32.728	6.983	15.144	1.00	58.26
ATOM	1034	O	ASN	A	127	33.132	8.096	15.487	1.00	58.82
ATOM	1035	CB	ASN	A	127	34.919	5.955	15.579	1.00	58.33
ATOM	1036	CG	ASN	A	127	35.959	4.889	15.347	1.00	62.63
ATOM	1037	OD1	ASN	A	127	35.660	3.697	15.490	1.00	64.16
ATOM	1038	ND2	ASN	A	127	37.179	5.307	15.008	1.00	60.87
ATOM	1039	N	THR	A	128	31.462	6.617	15.180	1.00	57.71
ATOM	1040	CA	THR	A	128	30.411	7.522	15.665	1.00	57.23
ATOM	1041	C	THR	A	128	29.652	6.846	16.795	1.00	56.48
ATOM	1042	O	THR	A	128	29.065	5.792	16.534	1.00	57.24
ATOM	1043	CB	THR	A	128	29.452	7.842	14.501	1.00	56.65
ATOM	1044	OG1	THR	A	128	30.208	8.579	13.536	1.00	57.99
ATOM	1045	CG2	THR	A	128	28.244	8.653	14.901	1.00	56.34
ATOM	1046	N	MET	A	129	29.705	7.406	18.002	1.00	54.99
ATOM	1047	CA	MET	A	129	29.082	6.817	19.175	1.00	52.19
ATOM	1048	C	MET	A	129	27.768	7.511	19.533	1.00	50.42
ATOM	1049	O	MET	A	129	27.588	8.705	19.319	1.00	48.93
ATOM	1050	CB	MET	A	129	30.009	6.909	20.391	1.00	58.00
ATOM	1051	CG	MET	A	129	31.164	5.934	20.458	1.00	62.68
ATOM	1052	SD	MET	A	129	30.652	4.263	20.904	1.00	68.26
ATOM	1053	CE	MET	A	129	29.906	4.518	22.510	1.00	68.01
ATOM	1054	N	HIS	A	130	26.859	6.735	20.126	1.00	49.01
ATOM	1055	CA	HIS	A	130	25.554	7.194	20.571	1.00	47.13
ATOM	1056	C	HIS	A	130	25.485	7.057	22.095	1.00	46.21
ATOM	1057	O	HIS	A	130	26.009	6.118	22.678	1.00	45.61
ATOM	1058	CB	HIS	A	130	24.436	6.345	19.956	1.00	53.82
ATOM	1059	CG	HIS	A	130	23.967	6.751	18.602	1.00	62.48
ATOM	1060	ND1	HIS	A	130	24.816	7.119	17.581	1.00	66.97
ATOM	1061	CD2	HIS	A	130	22.711	6.825	18.084	1.00	65.45
ATOM	1062	CE1	HIS	A	130	24.114	7.424	16.505	1.00	67.80
ATOM	1063	NE2	HIS	A	130	22.831	7.252	16.784	1.00	68.13
ATOM	1064	N	TYR	A	131	24.998	8.097	22.775	1.00	43.95
ATOM	1065	CA	TYR	A	131	24.923	8.130	24.227	1.00	42.51
ATOM	1066	C	TYR	A	131	23.536	8.666	24.576	1.00	41.94
ATOM	1067	O	TYR	A	131	22.956	9.497	23.829	1.00	41.77
ATOM	1068	CB	TYR	A	131	25.948	9.151	24.762	1.00	42.89
ATOM	1069	CG	TYR	A	131	27.390	8.830	24.392	1.00	42.97
ATOM	1070	CD1	TYR	A	131	27.910	9.421	23.240	1.00	42.76
ATOM	1071	CD2	TYR	A	131	28.205	7.993	25.131	1.00	43.24
ATOM	1072	CE1	TYR	A	131	29.207	9.187	22.828	1.00	44.91
ATOM	1073	CE2	TYR	A	131	29.502	7.765	24.728	1.00	45.47
ATOM	1074	CZ	TYR	A	131	29.991	8.365	23.587	1.00	46.72
ATOM	1075	OH	TYR	A	131	31.295	8.087	23.222	1.00	49.71
ATOM	1076	N	THR	A	132	22.979	8.297	25.721	1.00	40.16
ATOM	1077	CA	THR	A	132	21.666	8.825	26.098	1.00	37.97
ATOM	1078	C	THR	A	132	21.835	9.967	27.066	1.00	37.49
ATOM	1079	O	THR	A	132	22.535	9.779	28.077	1.00	38.05
ATOM	1080	CB	THR	A	132	20.792	7.731	26.746	1.00	38.81
ATOM	1081	OG1	THR	A	132	20.603	6.712	25.757	1.00	36.51
ATOM	1082	CG2	THR	A	132	19.452	8.267	27.216	1.00	36.18
ATOM	1083	N	ASN	A	133	21.212	11.104	26.792	1.00	35.61
ATOM	1084	CA	ASN	A	133	21.188	12.167	27.803	1.00	36.33
ATOM	1085	C	ASN	A	133	19.749	12.266	28.321	1.00	35.53
ATOM	1086	O	ASN	A	133	18.880	11.616	27.771	1.00	35.34

ATOM	1087	CB	ASN	A	133	21.662	13.500	27.280	1.00	36.82
ATOM	1088	CG	ASN	A	133	22.055	14.518	28.327	1.00	42.70
ATOM	1089	OD1	ASN	A	133	22.192	15.696	27.956	1.00	44.62
ATOM	1090	ND2	ASN	A	133	22.275	14.088	29.562	1.00	37.77
ATOM	1091	N	TRP	A	134	19.546	12.925	29.444	1.00	35.65
ATOM	1092	CA	TRP	A	134	18.238	12.908	30.127	1.00	36.02
ATOM	1093	C	TRP	A	134	17.856	14.318	30.510	1.00	36.37
ATOM	1094	O	TRP	A	134	18.686	15.002	31.095	1.00	37.57
ATOM	1095	CB	TRP	A	134	18.363	12.078	31.423	1.00	34.98
ATOM	1096	CG	TRP	A	134	18.900	10.691	31.221	1.00	35.16
ATOM	1097	CD1	TRP	A	134	20.214	10.320	31.363	1.00	36.78
ATOM	1098	CD2	TRP	A	134	18.190	9.511	30.845	1.00	37.83
ATOM	1099	NE1	TRP	A	134	20.350	8.987	31.103	1.00	33.83
ATOM	1100	CE2	TRP	A	134	19.121	8.458	30.802	1.00	34.86
ATOM	1101	CE3	TRP	A	134	16.836	9.240	30.593	1.00	35.07
ATOM	1102	CZ2	TRP	A	134	18.770	7.136	30.516	1.00	36.92
ATOM	1103	CZ3	TRP	A	134	16.498	7.932	30.308	1.00	39.28
ATOM	1104	CH2	TRP	A	134	17.449	6.905	30.240	1.00	38.59
ATOM	1105	N	THR	A	135	16.634	14.807	30.259	1.00	36.82
ATOM	1106	CA	THR	A	135	16.349	16.149	30.758	1.00	36.51
ATOM	1107	C	THR	A	135	16.094	16.125	32.270	1.00	37.13
ATOM	1108	O	THR	A	135	16.234	17.149	32.927	1.00	35.77
ATOM	1109	CB	THR	A	135	15.214	16.871	30.031	1.00	41.31
ATOM	1110	OG1	THR	A	135	13.979	16.175	30.224	1.00	39.42
ATOM	1111	CG2	THR	A	135	15.461	16.910	28.512	1.00	43.30
ATOM	1112	N	HIS	A	136	15.650	15.007	32.831	1.00	36.50
ATOM	1113	CA	HIS	A	136	15.236	14.974	34.227	1.00	37.55
ATOM	1114	C	HIS	A	136	16.017	13.856	34.948	1.00	36.41
ATOM	1115	O	HIS	A	136	15.783	12.717	34.570	1.00	37.39
ATOM	1116	CB	HIS	A	136	13.731	14.716	34.346	1.00	42.28
ATOM	1117	CG	HIS	A	136	12.843	15.884	34.044	1.00	45.85
ATOM	1118	ND1	HIS	A	136	12.928	16.585	32.850	1.00	44.57
ATOM	1119	CD2	HIS	A	136	11.847	16.467	34.751	1.00	47.41
ATOM	1120	CE1	HIS	A	136	12.039	17.564	32.853	1.00	45.33
ATOM	1121	NE2	HIS	A	136	11.362	17.512	33.987	1.00	49.47
ATOM	1122	N	ILE	A	137	16.941	14.223	35.827	1.00	35.44
ATOM	1123	CA	ILE	A	137	17.696	13.165	36.526	1.00	34.42
ATOM	1124	C	ILE	A	137	17.396	13.291	38.023	1.00	34.06
ATOM	1125	O	ILE	A	137	17.573	14.396	38.537	1.00	34.29
ATOM	1126	CB	ILE	A	137	19.209	13.314	36.268	1.00	33.02
ATOM	1127	CG1	ILE	A	137	19.527	13.053	34.780	1.00	33.98
ATOM	1128	CG2	ILE	A	137	19.995	12.315	37.126	1.00	34.85
ATOM	1129	CD1	ILE	A	137	20.948	13.484	34.427	1.00	35.15
ATOM	1130	N	TYR	A	138	16.902	12.217	38.643	1.00	33.90
ATOM	1131	CA	TYR	A	138	16.497	12.371	40.067	1.00	34.35
ATOM	1132	C	TYR	A	138	17.618	11.920	40.998	1.00	34.35
ATOM	1133	O	TYR	A	138	17.925	10.740	40.954	1.00	35.52
ATOM	1134	CB	TYR	A	138	15.196	11.604	40.319	1.00	35.05
ATOM	1135	CG	TYR	A	138	14.075	12.281	39.524	1.00	37.41
ATOM	1136	CD1	TYR	A	138	13.904	11.924	38.203	1.00	38.75
ATOM	1137	CD2	TYR	A	138	13.272	13.267	40.084	1.00	40.04
ATOM	1138	CE1	TYR	A	138	12.922	12.525	37.431	1.00	39.64
ATOM	1139	CE2	TYR	A	138	12.281	13.870	39.308	1.00	41.81
ATOM	1140	CZ	TYR	A	138	12.128	13.492	37.999	1.00	41.16
ATOM	1141	OH	TYR	A	138	11.171	14.050	37.192	1.00	43.58
ATOM	1142	N	ILE	A	139	18.255	12.823	41.721	1.00	34.48
ATOM	1143	CA	ILE	A	139	19.360	12.458	42.607	1.00	35.01
ATOM	1144	C	ILE	A	139	18.756	12.127	43.996	1.00	34.60
ATOM	1145	O	ILE	A	139	18.312	13.089	44.613	1.00	35.20
ATOM	1146	CB	ILE	A	139	20.353	13.612	42.774	1.00	34.61
ATOM	1147	CG1	ILE	A	139	20.926	14.098	41.421	1.00	38.01
ATOM	1148	CG2	ILE	A	139	21.546	13.200	43.637	1.00	37.55
ATOM	1149	CD1	ILE	A	139	21.487	12.956	40.588	1.00	38.91

ATOM	1150	N	CYS	A	140	18.581	10.861	44.301	1.00 35.26
ATOM	1151	CA	CYS	A	140	17.938	10.511	45.590	1.00 37.11
ATOM	1152	C	CYS	A	140	18.952	10.174	46.664	1.00 37.66
ATOM	1153	O	CYS	A	140	19.865	9.384	46.448	1.00 37.82
ATOM	1154	CB	CYS	A	140	17.078	9.251	45.411	1.00 42.45
ATOM	1155	SG	CYS	A	140	15.483	9.689	44.680	1.00 49.17
ATOM	1156	N	GLU	A	141	18.799	10.796	47.831	1.00 37.14
ATOM	1157	CA	GLU	A	141	19.664	10.484	48.966	1.00 37.88
ATOM	1158	C	GLU	A	141	18.845	9.929	50.125	1.00 36.63
ATOM	1159	O	GLU	A	141	17.678	9.579	49.925	1.00 35.72
ATOM	1160	CB	GLU	A	141	20.509	11.709	49.297	1.00 43.42
ATOM	1161	CG	GLU	A	141	21.392	12.145	48.129	1.00 53.61
ATOM	1162	CD	GLU	A	141	22.122	13.446	48.352	1.00 58.09
ATOM	1163	OE1	GLU	A	141	21.544	14.528	48.139	1.00 57.53
ATOM	1164	OE2	GLU	A	141	23.308	13.339	48.747	1.00 64.14
ATOM	1165	N	GLU	A	142	19.445	9.883	51.315	1.00 36.78
ATOM	1166	CA	GLU	A	142	18.783	9.263	52.479	1.00 36.84
ATOM	1167	C	GLU	A	142	17.515	9.941	52.907	1.00 35.85
ATOM	1168	O	GLU	A	142	16.496	9.267	53.166	1.00 36.59
ATOM	1169	CB	GLU	A	142	19.780	9.360	53.654	1.00 43.10
ATOM	1170	CG	GLU	A	142	21.150	8.763	53.466	1.00 54.03
ATOM	1171	CD	GLU	A	142	22.322	9.696	53.311	1.00 60.55
ATOM	1172	OE1	GLU	A	142	22.260	10.679	52.543	1.00 59.21
ATOM	1173	OE2	GLU	A	142	23.401	9.470	53.924	1.00 64.17
ATOM	1174	N	ALA	A	143	17.477	11.272	52.922	1.00 34.96
ATOM	1175	CA	ALA	A	143	16.241	11.960	53.308	1.00 36.52
ATOM	1176	C	ALA	A	143	15.739	12.999	52.312	1.00 36.98
ATOM	1177	O	ALA	A	143	15.239	14.019	52.787	1.00 38.22
ATOM	1178	CB	ALA	A	143	16.560	12.620	54.652	1.00 34.45
ATOM	1179	N	SER	A	144	16.163	12.881	51.031	1.00 36.01
ATOM	1180	CA	SER	A	144	15.754	13.884	50.048	1.00 35.70
ATOM	1181	C	SER	A	144	15.959	13.477	48.583	1.00 35.68
ATOM	1182	O	SER	A	144	16.665	12.520	48.259	1.00 34.04
ATOM	1183	CB	SER	A	144	16.607	15.158	50.246	1.00 39.92
ATOM	1184	OG	SER	A	144	17.965	14.791	49.965	1.00 46.64
ATOM	1185	N	VAL	A	145	15.361	14.287	47.712	1.00 36.14
ATOM	1186	CA	VAL	A	145	15.576	14.054	46.260	1.00 35.49
ATOM	1187	C	VAL	A	145	15.546	15.410	45.563	1.00 36.78
ATOM	1188	O	VAL	A	145	14.806	16.307	45.979	1.00 34.89
ATOM	1189	CB	VAL	A	145	14.580	13.058	45.707	1.00 36.75
ATOM	1190	CG1	VAL	A	145	13.141	13.446	46.028	1.00 36.76
ATOM	1191	CG2	VAL	A	145	14.730	12.908	44.192	1.00 37.20
ATOM	1192	N	THR	A	146	16.453	15.595	44.600	1.00 37.23
ATOM	1193	CA	THR	A	146	16.434	16.814	43.769	1.00 39.11
ATOM	1194	C	THR	A	146	16.529	16.390	42.297	1.00 39.36
ATOM	1195	O	THR	A	146	17.361	15.521	41.981	1.00 39.50
ATOM	1196	CB	THR	A	146	17.709	17.657	44.040	1.00 43.57
ATOM	1197	OG1	THR	A	146	17.833	17.886	45.432	1.00 49.29
ATOM	1198	CG2	THR	A	146	17.686	18.953	43.244	1.00 46.55
ATOM	1199	N	VAL	A	147	15.699	16.998	41.454	1.00 39.48
ATOM	1200	CA	VAL	A	147	15.774	16.719	40.017	1.00 38.72
ATOM	1201	C	VAL	A	147	16.800	17.682	39.433	1.00 39.04
ATOM	1202	O	VAL	A	147	16.921	18.842	39.851	1.00 38.28
ATOM	1203	CB	VAL	A	147	14.451	16.800	39.268	1.00 40.51
ATOM	1204	CG1	VAL	A	147	13.871	18.209	39.197	1.00 42.34
ATOM	1205	CG2	VAL	A	147	14.532	16.183	37.873	1.00 36.37
ATOM	1206	N	VAL	A	148	17.711	17.103	38.634	1.00 39.16
ATOM	1207	CA	VAL	A	148	18.685	17.909	37.910	1.00 38.86
ATOM	1208	C	VAL	A	148	18.569	17.615	36.406	1.00 38.03
ATOM	1209	O	VAL	A	148	18.093	16.554	35.994	1.00 38.38
ATOM	1210	CB	VAL	A	148	20.117	17.663	38.437	1.00 37.94
ATOM	1211	CG1	VAL	A	148	20.196	17.921	39.948	1.00 37.81
ATOM	1212	CG2	VAL	A	148	20.543	16.227	38.135	1.00 39.08

ATOM	1213	N	GLU	A	149	19.105	18.521	35.575	1.00 37.21
ATOM	1214	CA	GLU	A	149	19.010	18.272	34.118	1.00 37.63
ATOM	1215	C	GLU	A	149	20.309	17.767	33.517	1.00 36.45
ATOM	1216	O	GLU	A	149	21.385	18.214	33.912	1.00 37.57
ATOM	1217	CB	GLU	A	149	18.519	19.530	33.403	1.00 48.95
ATOM	1218	CG	GLU	A	149	19.598	20.527	33.046	1.00 53.64
ATOM	1219	CD	GLU	A	149	19.100	21.544	32.022	1.00 58.00
ATOM	1220	OE1	GLU	A	149	19.440	22.716	32.229	1.00 55.36
ATOM	1221	OE2	GLU	A	149	18.363	21.228	31.067	1.00 61.49
ATOM	1222	N	GLY	A	150	20.200	16.861	32.559	1.00 37.43
ATOM	1223	CA	GLY	A	150	21.399	16.289	31.923	1.00 37.28
ATOM	1224	C	GLY	A	150	21.910	17.392	30.970	1.00 37.55
ATOM	1225	O	GLY	A	150	21.071	18.016	30.338	1.00 37.62
ATOM	1226	N	GLN	A	151	23.181	17.714	31.014	1.00 37.21
ATOM	1227	CA	GLN	A	151	23.713	18.812	30.210	1.00 36.92
ATOM	1228	C	GLN	A	151	24.833	18.247	29.331	1.00 37.46
ATOM	1229	O	GLN	A	151	25.351	17.166	29.610	1.00 35.27
ATOM	1230	CB	GLN	A	151	24.280	19.937	31.078	1.00 37.56
ATOM	1231	CG	GLN	A	151	23.177	20.667	31.852	1.00 43.46
ATOM	1232	CD	GLN	A	151	23.691	21.877	32.581	1.00 48.78
ATOM	1233	OE1	GLN	A	151	23.987	22.896	31.946	1.00 49.56
ATOM	1234	NE2	GLN	A	151	23.820	21.769	33.905	1.00 44.12
ATOM	1235	N	VAL	A	152	25.173	19.028	28.294	1.00 36.05
ATOM	1236	CA	VAL	A	152	26.097	18.488	27.284	1.00 36.80
ATOM	1237	C	VAL	A	152	27.209	19.494	26.986	1.00 37.21
ATOM	1238	O	VAL	A	152	26.949	20.667	26.795	1.00 36.72
ATOM	1239	CB	VAL	A	152	25.385	18.266	25.921	1.00 40.17
ATOM	1240	CG1	VAL	A	152	26.394	17.345	25.148	1.00 37.05
ATOM	1241	CG2	VAL	A	152	24.181	17.350	26.088	1.00 42.64
ATOM	1242	N	ASP	A	153	28.420	19.032	27.005	1.00 37.01
ATOM	1243	CA	ASP	A	153	29.712	19.530	26.819	1.00 37.91
ATOM	1244	C	ASP	A	153	30.452	19.060	25.554	1.00 36.17
ATOM	1245	O	ASP	A	153	30.094	18.059	24.955	1.00 37.68
ATOM	1246	CB	ASP	A	153	30.713	19.123	28.066	1.00 30.79
ATOM	1247	CG	ASP	A	153	30.890	20.514	28.634	1.00 39.47
ATOM	1248	OD1	ASP	A	153	30.469	21.441	27.840	1.00 53.60
ATOM	1249	OD2	ASP	A	153	31.411	20.767	29.695	1.00 41.06
ATOM	1250	N	TYR	A	154	31.550	19.785	25.263	1.00 36.73
ATOM	1251	CA	TYR	A	154	32.497	19.232	24.299	1.00 38.06
ATOM	1252	C	TYR	A	154	33.107	17.950	24.912	1.00 38.77
ATOM	1253	O	TYR	A	154	33.386	16.934	24.276	1.00 38.93
ATOM	1254	CB	TYR	A	154	33.624	20.200	23.920	1.00 38.36
ATOM	1255	CG	TYR	A	154	34.637	19.489	23.038	1.00 38.72
ATOM	1256	CD1	TYR	A	154	34.295	19.193	21.714	1.00 39.88
ATOM	1257	CD2	TYR	A	154	35.875	19.104	23.514	1.00 39.51
ATOM	1258	CE1	TYR	A	154	35.184	18.532	20.873	1.00 39.95
ATOM	1259	CE2	TYR	A	154	36.759	18.454	22.687	1.00 41.22
ATOM	1260	CZ	TYR	A	154	36.412	18.174	21.376	1.00 41.17
ATOM	1261	OH	TYR	A	154	37.332	17.516	20.610	1.00 42.16
ATOM	1262	N	TYR	A	155	33.319	18.027	26.224	1.00 38.13
ATOM	1263	CA	TYR	A	155	33.883	16.968	27.018	1.00 38.84
ATOM	1264	C	TYR	A	155	32.959	15.819	27.350	1.00 37.80
ATOM	1265	O	TYR	A	155	33.530	14.735	27.543	1.00 37.77
ATOM	1266	CB	TYR	A	155	34.500	17.518	28.323	1.00 40.03
ATOM	1267	CG	TYR	A	155	35.364	18.745	28.031	1.00 43.75
ATOM	1268	CD1	TYR	A	155	34.854	20.021	28.230	1.00 44.64
ATOM	1269	CD2	TYR	A	155	36.655	18.604	27.562	1.00 44.86
ATOM	1270	CE1	TYR	A	155	35.628	21.136	27.950	1.00 46.55
ATOM	1271	CE2	TYR	A	155	37.440	19.709	27.271	1.00 46.37
ATOM	1272	CZ	TYR	A	155	36.920	20.963	27.485	1.00 48.04
ATOM	1273	OH	TYR	A	155	37.708	22.064	27.230	1.00 50.62
ATOM	1274	N	GLY	A	156	31.651	16.005	27.491	1.00 36.89
ATOM	1275	CA	GLY	A	156	30.784	14.894	27.833	1.00 36.27

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ATOM   1276  C   GLY A 156      29.374  15.297  28.278  1.00 36.29
ATOM   1277  O   GLY A 156      28.845  16.351  27.962  1.00 36.73
ATOM   1278  N   LEU A 157      28.737  14.367  28.989  1.00 35.47
ATOM   1279  CA  LEU A 157      27.410  14.593  29.547  1.00 36.71
ATOM   1280  C   LEU A 157      27.570  14.782  31.061  1.00 36.98
ATOM   1281  O   LEU A 157      28.299  14.009  31.703  1.00 37.91
ATOM   1282  CB  LEU A 157      26.472  13.404  29.348  1.00 36.06
ATOM   1283  CG  LEU A 157      26.409  12.902  27.878  1.00 39.11
ATOM   1284  CD1 LEU A 157      25.362  11.777  27.835  1.00 40.34
ATOM   1285  CD2 LEU A 157      25.944  14.021  26.948  1.00 37.66
ATOM   1286  N   TYR A 158      26.860  15.773  31.583  1.00 36.59
ATOM   1287  CA  TYR A 158      27.043  16.018  33.020  1.00 37.29
ATOM   1288  C   TYR A 158      25.778  16.579  33.654  1.00 37.06
ATOM   1289  O   TYR A 158      24.813  16.941  32.968  1.00 36.78
ATOM   1290  CB  TYR A 158      28.202  17.007  33.172  1.00 37.24
ATOM   1291  CG  TYR A 158      27.948  18.410  32.664  1.00 38.25
ATOM   1292  CD1 TYR A 158      27.547  19.427  33.526  1.00 37.59
ATOM   1293  CD2 TYR A 158      28.158  18.721  31.322  1.00 38.51
ATOM   1294  CE1 TYR A 158      27.355  20.718  33.056  1.00 38.42
ATOM   1295  CE2 TYR A 158      27.955  20.009  30.839  1.00 38.37
ATOM   1296  CZ  TYR A 158      27.573  21.006  31.711  1.00 38.61
ATOM   1297  OH  TYR A 158      27.359  22.290  31.260  1.00 37.90
ATOM   1298  N   TYR A 159      25.799  16.661  34.979  1.00 36.65
ATOM   1299  CA  TYR A 159      24.758  17.394  35.694  1.00 37.45
ATOM   1300  C   TYR A 159      25.493  18.169  36.801  1.00 37.16
ATOM   1301  O   TYR A 159      26.659  17.920  37.045  1.00 37.16
ATOM   1302  CB  TYR A 159      23.638  16.543  36.301  1.00 37.42
ATOM   1303  CG  TYR A 159      24.161  15.441  37.222  1.00 37.53
ATOM   1304  CD1 TYR A 159      24.429  14.181  36.732  1.00 39.31
ATOM   1305  CD2 TYR A 159      24.352  15.689  38.574  1.00 38.15
ATOM   1306  CE1 TYR A 159      24.902  13.169  37.564  1.00 39.89
ATOM   1307  CE2 TYR A 159      24.823  14.699  39.407  1.00 38.54
ATOM   1308  CZ  TYR A 159      25.101  13.454  38.893  1.00 39.58
ATOM   1309  OH  TYR A 159      25.613  12.488  39.741  1.00 40.63
ATOM   1310  N   VAL A 160      24.779  19.122  37.356  1.00 36.88
ATOM   1311  CA  VAL A 160      25.251  19.943  38.452  1.00 38.20
ATOM   1312  C   VAL A 160      24.277  19.714  39.629  1.00 38.68
ATOM   1313  O   VAL A 160      23.078  19.922  39.514  1.00 38.89
ATOM   1314  CB  VAL A 160      25.295  21.439  38.094  1.00 41.01
ATOM   1315  CG1 VAL A 160      25.815  22.251  39.288  1.00 39.83
ATOM   1316  CG2 VAL A 160      26.254  21.687  36.916  1.00 36.61
ATOM   1317  N   HIS A 161      24.818  19.208  40.708  1.00 39.08
ATOM   1318  CA  HIS A 161      24.018  18.916  41.919  1.00 39.84
ATOM   1319  C   HIS A 161      24.734  19.569  43.095  1.00 39.51
ATOM   1320  O   HIS A 161      25.900  19.316  43.322  1.00 38.92
ATOM   1321  CB  HIS A 161      23.939  17.418  42.140  1.00 37.10
ATOM   1322  CG  HIS A 161      23.189  16.976  43.377  1.00 36.87
ATOM   1323  ND1 HIS A 161      21.908  17.363  43.665  1.00 42.27
ATOM   1324  CD2 HIS A 161      23.571  16.163  44.374  1.00 38.66
ATOM   1325  CE1 HIS A 161      21.508  16.811  44.805  1.00 34.42
ATOM   1326  NE2 HIS A 161      22.503  16.079  45.262  1.00 40.76
ATOM   1327  N   GLU A 162      24.031  20.404  43.832  1.00 41.45
ATOM   1328  CA  GLU A 162      24.557  21.115  44.998  1.00 43.07
ATOM   1329  C   GLU A 162      25.795  21.928  44.616  1.00 42.85
ATOM   1330  O   GLU A 162      26.806  21.828  45.304  1.00 43.43
ATOM   1331  CB  GLU A 162      24.930  20.138  46.121  1.00 46.97
ATOM   1332  CG  GLU A 162      23.750  19.235  46.415  1.00 59.55
ATOM   1333  CD  GLU A 162      23.494  18.891  47.854  1.00 61.68
ATOM   1334  OE1 GLU A 162      22.551  19.508  48.387  1.00 66.02
ATOM   1335  OE2 GLU A 162      24.226  18.027  48.364  1.00 65.49
ATOM   1336  N   GLY A 163      25.786  22.518  43.432  1.00 43.79
ATOM   1337  CA  GLY A 163      26.930  23.253  42.929  1.00 43.51
ATOM   1338  C   GLY A 163      28.023  22.409  42.306  1.00 43.73
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ATOM   1339  O   GLY A 163      28.958  23.011  41.746  1.00 43.41
ATOM   1340  N   ILE A 164      27.986  21.079  42.371  1.00 42.17
ATOM   1341  CA  ILE A 164      29.078  20.258  41.896  1.00 41.52
ATOM   1342  C   ILE A 164      28.743  19.687  40.513  1.00 41.11
ATOM   1343  O   ILE A 164      27.677  19.110  40.314  1.00 40.21
ATOM   1344  CB  ILE A 164      29.442  19.081  42.820  1.00 41.77
ATOM   1345  CG1 ILE A 164      29.730  19.597  44.228  1.00 46.60
ATOM   1346  CG2 ILE A 164      30.651  18.346  42.258  1.00 43.25
ATOM   1347  CD1 ILE A 164      29.708  18.526  45.303  1.00 50.89
ATOM   1348  N   ARG A 165      29.613  20.004  39.561  1.00 40.27
ATOM   1349  CA  ARG A 165      29.428  19.508  38.202  1.00 40.37
ATOM   1350  C   ARG A 165      29.979  18.082  38.132  1.00 40.18
ATOM   1351  O   ARG A 165      31.139  17.889  38.436  1.00 40.87
ATOM   1352  CB  ARG A 165      30.211  20.389  37.205  1.00 43.98
ATOM   1353  CG  ARG A 165      30.190  19.775  35.799  1.00 48.81
ATOM   1354  CD  ARG A 165      31.056  20.614  34.844  1.00 50.67
ATOM   1355  NE  ARG A 165      30.374  21.882  34.644  1.00 54.50
ATOM   1356  CZ  ARG A 165      30.245  22.592  33.535  1.00 51.25
ATOM   1357  NH1 ARG A 165      30.788  22.211  32.399  1.00 52.55
ATOM   1358  NH2 ARG A 165      29.552  23.727  33.612  1.00 46.13
ATOM   1359  N   THR A 166      29.159  17.127  37.747  1.00 38.84
ATOM   1360  CA  THR A 166      29.502  15.722  37.710  1.00 37.91
ATOM   1361  C   THR A 166      29.318  15.152  36.310  1.00 36.66
ATOM   1362  O   THR A 166      28.167  15.109  35.857  1.00 36.77
ATOM   1363  CB  THR A 166      28.621  14.911  38.700  1.00 42.71
ATOM   1364  OG1 THR A 166      28.895  15.399  40.034  1.00 43.09
ATOM   1365  CG2 THR A 166      28.934  13.427  38.662  1.00 40.93
ATOM   1366  N   TYR A 167      30.398  14.733  35.667  1.00 36.29
ATOM   1367  CA  TYR A 167      30.309  14.112  34.342  1.00 36.95
ATOM   1368  C   TYR A 167      29.970  12.639  34.466  1.00 37.76
ATOM   1369  O   TYR A 167      30.561  11.961  35.335  1.00 39.69
ATOM   1370  CB  TYR A 167      31.611  14.231  33.518  1.00 37.91
ATOM   1371  CG  TYR A 167      31.797  15.617  32.933  1.00 38.45
ATOM   1372  CD1 TYR A 167      32.311  16.637  33.726  1.00 39.32
ATOM   1373  CD2 TYR A 167      31.397  15.937  31.646  1.00 39.69
ATOM   1374  CE1 TYR A 167      32.458  17.919  33.243  1.00 38.98
ATOM   1375  CE2 TYR A 167      31.535  17.214  31.133  1.00 39.08
ATOM   1376  CZ  TYR A 167      32.064  18.201  31.946  1.00 40.35
ATOM   1377  OH  TYR A 167      32.216  19.488  31.494  1.00 39.61
ATOM   1378  N   PHE A 168      28.924  12.172  33.821  1.00 37.39
ATOM   1379  CA  PHE A 168      28.547  10.772  33.818  1.00 38.28
ATOM   1380  C   PHE A 168      28.987  10.058  32.559  1.00 39.29
ATOM   1381  O   PHE A 168      28.980   8.825  32.494  1.00 38.30
ATOM   1382  CB  PHE A 168      27.085  10.508  34.167  1.00 38.07
ATOM   1383  CG  PHE A 168      26.068  11.226  33.320  1.00 34.93
ATOM   1384  CD1 PHE A 168      25.596  10.661  32.153  1.00 36.11
ATOM   1385  CD2 PHE A 168      25.609  12.470  33.722  1.00 35.04
ATOM   1386  CE1 PHE A 168      24.656  11.337  31.364  1.00 34.93
ATOM   1387  CE2 PHE A 168      24.672  13.140  32.951  1.00 35.38
ATOM   1388  CZ  PHE A 168      24.215  12.564  31.799  1.00 30.80
ATOM   1389  N   VAL A 169      29.331  10.849  31.524  1.00 39.59
ATOM   1390  CA  VAL A 169      30.019  10.310  30.354  1.00 40.03
ATOM   1391  C   VAL A 169      31.149  11.322  30.039  1.00 41.32
ATOM   1392  O   VAL A 169      30.904  12.530  30.018  1.00 39.98
ATOM   1393  CB  VAL A 169      29.136  10.155  29.112  1.00 39.59
ATOM   1394  CG1 VAL A 169      29.988   9.684  27.917  1.00 41.55
ATOM   1395  CG2 VAL A 169      28.019   9.107  29.242  1.00 38.14
ATOM   1396  N   GLN A 170      32.377  10.844  29.870  1.00 41.92
ATOM   1397  CA  GLN A 170      33.464  11.693  29.396  1.00 42.70
ATOM   1398  C   GLN A 170      33.833  11.215  27.990  1.00 43.33
ATOM   1399  O   GLN A 170      34.348  10.097  27.861  1.00 43.22
ATOM   1400  CB  GLN A 170      34.696  11.627  30.293  1.00 39.48
ATOM   1401  CG  GLN A 170      34.448  12.220  31.676  1.00 45.31
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ATOM   1402  CD  GLN A 170      35.691  12.212  32.542  1.00 46.68
ATOM   1403  OE1 GLN A 170      35.649  11.848  33.717  1.00 52.69
ATOM   1404  NE2 GLN A 170      36.816  12.618  31.998  1.00 47.58
ATOM   1405  N   PHE A 171      33.678  12.076  26.982  1.00 43.04
ATOM   1406  CA  PHE A 171      33.884  11.606  25.629  1.00 44.34
ATOM   1407  C   PHE A 171      35.302  11.186  25.340  1.00 45.84
ATOM   1408  O   PHE A 171      35.508  10.343  24.446  1.00 45.10
ATOM   1409  CB  PHE A 171      33.422  12.612  24.597  1.00 39.68
ATOM   1410  CG  PHE A 171      31.961  12.978  24.639  1.00 38.24
ATOM   1411  CD1 PHE A 171      31.016  11.986  24.875  1.00 40.47
ATOM   1412  CD2 PHE A 171      31.530  14.269  24.412  1.00 35.50
ATOM   1413  CE1 PHE A 171      29.673  12.310  24.905  1.00 37.70
ATOM   1414  CE2 PHE A 171      30.187  14.604  24.441  1.00 37.98
ATOM   1415  CZ  PHE A 171      29.248  13.621  24.690  1.00 37.99
ATOM   1416  N   LYS A 172      36.287  11.662  26.080  1.00 45.69
ATOM   1417  CA  LYS A 172      37.660  11.223  25.889  1.00 47.54
ATOM   1418  C   LYS A 172      37.949   9.748  26.138  1.00 48.27
ATOM   1419  O   LYS A 172      38.884   9.175  25.570  1.00 48.26
ATOM   1420  CB  LYS A 172      38.594  12.102  26.708  1.00 52.42
ATOM   1421  CG  LYS A 172      40.022  12.159  26.201  1.00 57.12
ATOM   1422  CD  LYS A 172      40.904  12.971  27.157  1.00 64.24
ATOM   1423  CE  LYS A 172      42.362  12.543  27.018  1.00 65.59
ATOM   1424  NZ  LYS A 172      43.304  13.691  26.949  1.00 65.87
ATOM   1425  N   ASP A 173      37.154   9.132  27.009  1.00 48.25
ATOM   1426  CA  ASP A 173      37.212   7.712  27.287  1.00 49.23
ATOM   1427  C   ASP A 173      36.954   6.925  26.007  1.00 49.36
ATOM   1428  O   ASP A 173      37.788   6.072  25.701  1.00 49.13
ATOM   1429  CB  ASP A 173      36.263   7.269  28.394  1.00 46.27
ATOM   1430  CG  ASP A 173      36.627   7.869  29.740  1.00 50.82
ATOM   1431  OD1 ASP A 173      35.740   8.056  30.605  1.00 51.86
ATOM   1432  OD2 ASP A 173      37.817   8.158  29.970  1.00 52.02
ATOM   1433  N   ASP A 174      35.901   7.144  25.248  1.00 49.89
ATOM   1434  CA  ASP A 174      35.671   6.430  24.007  1.00 50.79
ATOM   1435  C   ASP A 174      36.647   6.784  22.897  1.00 52.00
ATOM   1436  O   ASP A 174      37.085   5.884  22.165  1.00 51.37
ATOM   1437  CB  ASP A 174      34.231   6.582  23.539  1.00 51.65
ATOM   1438  CG  ASP A 174      33.276   5.662  24.274  1.00 51.83
ATOM   1439  OD1 ASP A 174      33.751   4.664  24.847  1.00 48.40
ATOM   1440  OD2 ASP A 174      32.060   5.942  24.269  1.00 52.72
ATOM   1441  N   ALA A 175      37.040   8.053  22.808  1.00 52.36
ATOM   1442  CA  ALA A 175      38.024   8.476  21.821  1.00 53.78
ATOM   1443  C   ALA A 175      39.362   7.759  21.964  1.00 54.22
ATOM   1444  O   ALA A 175      39.999   7.417  20.974  1.00 54.32
ATOM   1445  CB  ALA A 175      38.226   9.986  21.910  1.00 51.67
ATOM   1446  N   GLU A 176      39.832   7.508  23.186  1.00 55.55
ATOM   1447  CA  GLU A 176      41.120   6.865  23.409  1.00 56.73
ATOM   1448  C   GLU A 176      41.015   5.357  23.234  1.00 57.74
ATOM   1449  O   GLU A 176      42.025   4.646  23.187  1.00 58.14
ATOM   1450  CB  GLU A 176      41.655   7.170  24.806  1.00 56.85
ATOM   1451  CG  GLU A 176      41.910   8.632  25.116  1.00 59.30
ATOM   1452  CD  GLU A 176      42.180   8.743  26.537  0.00 99.00
ATOM   1453  OE1 GLU A 176      41.740   8.063  27.454  0.00 99.00
ATOM   1454  OE2 GLU A 176      43.073   9.574  26.687  0.00 99.00
ATOM   1455  N   LYS A 177      39.790   4.852  23.170  1.00 58.44
ATOM   1456  CA  LYS A 177      39.555   3.420  23.024  1.00 59.70
ATOM   1457  C   LYS A 177      39.312   3.069  21.561  1.00 60.20
ATOM   1458  O   LYS A 177      39.326   1.895  21.198  1.00 60.71
ATOM   1459  CB  LYS A 177      38.350   3.040  23.887  1.00 63.58
ATOM   1460  CG  LYS A 177      38.054   1.569  24.029  1.00 67.87
ATOM   1461  CD  LYS A 177      37.047   1.277  25.140  1.00 70.02
ATOM   1462  CE  LYS A 177      36.872  -0.235  25.242  1.00 73.46
ATOM   1463  NZ  LYS A 177      36.221  -0.638  26.517  1.00 75.57
ATOM   1464  N   TYR A 178      38.908   4.057  20.758  1.00 60.36
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ATOM	1465	CA	TYR	A	178	38.551	3.798	19.381	1.00	61.69
ATOM	1466	C	TYR	A	178	39.369	4.563	18.361	1.00	62.23
ATOM	1467	O	TYR	A	178	39.821	3.923	17.409	1.00	63.37
ATOM	1468	CB	TYR	A	178	37.057	3.988	19.100	1.00	61.34
ATOM	1469	CG	TYR	A	178	36.139	3.197	20.010	1.00	61.39
ATOM	1470	CD1	TYR	A	178	36.249	1.811	20.081	1.00	62.10
ATOM	1471	CD2	TYR	A	178	35.189	3.821	20.798	1.00	61.28
ATOM	1472	CE1	TYR	A	178	35.440	1.072	20.929	1.00	62.32
ATOM	1473	CE2	TYR	A	178	34.378	3.097	21.651	1.00	62.22
ATOM	1474	CZ	TYR	A	178	34.505	1.723	21.707	1.00	62.51
ATOM	1475	OH	TYR	A	178	33.696	0.989	22.540	1.00	62.15
ATOM	1476	N	SER	A	179	39.573	5.858	18.525	1.00	62.95
ATOM	1477	CA	SER	A	179	40.159	6.703	17.498	1.00	64.19
ATOM	1478	C	SER	A	179	41.662	6.923	17.631	1.00	64.98
ATOM	1479	O	SER	A	179	42.279	6.550	18.630	1.00	64.79
ATOM	1480	CB	SER	A	179	39.470	8.077	17.505	1.00	65.34
ATOM	1481	OG	SER	A	179	39.982	8.923	16.491	1.00	69.64
ATOM	1482	N	LYS	A	180	42.254	7.552	16.609	1.00	65.75
ATOM	1483	CA	LYS	A	180	43.672	7.876	16.658	1.00	66.93
ATOM	1484	C	LYS	A	180	43.886	9.316	17.107	1.00	67.25
ATOM	1485	O	LYS	A	180	44.806	9.591	17.887	1.00	67.85
ATOM	1486	CB	LYS	A	180	44.431	7.615	15.360	1.00	69.83
ATOM	1487	CG	LYS	A	180	45.938	7.673	15.581	1.00	73.65
ATOM	1488	CD	LYS	A	180	46.681	8.326	14.427	1.00	76.04
ATOM	1489	CE	LYS	A	180	48.016	8.889	14.887	1.00	75.99
ATOM	1490	NZ	LYS	A	180	47.829	10.056	15.790	1.00	78.28
ATOM	1491	N	ASN	A	181	43.017	10.216	16.652	1.00	66.93
ATOM	1492	CA	ASN	A	181	43.126	11.609	17.113	1.00	66.52
ATOM	1493	C	ASN	A	181	42.128	11.842	18.240	1.00	65.58
ATOM	1494	O	ASN	A	181	41.133	11.131	18.348	1.00	65.86
ATOM	1495	CB	ASN	A	181	43.174	12.454	16.113	0.00	99.00
ATOM	1496	CG	ASN	A	181	44.528	12.902	15.624	0.00	99.00
ATOM	1497	OD1	ASN	A	181	45.545	12.248	15.833	0.00	99.00
ATOM	1498	ND2	ASN	A	181	44.525	14.056	14.935	0.00	99.00
ATOM	1499	N	LYS	A	182	42.432	12.756	19.155	1.00	65.06
ATOM	1500	CA	LYS	A	182	41.483	13.086	20.232	1.00	62.47
ATOM	1501	C	LYS	A	182	40.755	14.370	19.855	1.00	60.44
ATOM	1502	O	LYS	A	182	40.951	15.405	20.491	1.00	60.89
ATOM	1503	CB	LYS	A	182	42.257	13.224	21.544	1.00	68.03
ATOM	1504	CG	LYS	A	182	41.462	13.626	22.774	1.00	70.69
ATOM	1505	CD	LYS	A	182	42.223	14.606	23.651	1.00	73.12
ATOM	1506	CE	LYS	A	182	41.360	15.246	24.718	1.00	73.28
ATOM	1507	NZ	LYS	A	182	40.729	16.534	24.325	1.00	74.63
ATOM	1508	N	VAL	A	183	40.007	14.401	18.761	1.00	58.04
ATOM	1509	CA	VAL	A	183	39.240	15.559	18.324	1.00	55.16
ATOM	1510	C	VAL	A	183	37.899	15.073	17.781	1.00	52.42
ATOM	1511	O	VAL	A	183	37.902	14.220	16.898	1.00	52.43
ATOM	1512	CB	VAL	A	183	39.936	16.462	17.302	1.00	58.84
ATOM	1513	CG1	VAL	A	183	38.965	17.219	16.395	1.00	61.12
ATOM	1514	CG2	VAL	A	183	40.809	17.504	18.010	1.00	60.87
ATOM	1515	N	TRP	A	184	36.785	15.581	18.302	1.00	49.48
ATOM	1516	CA	TRP	A	184	35.495	15.042	17.878	1.00	45.59
ATOM	1517	C	TRP	A	184	34.490	16.159	17.706	1.00	44.01
ATOM	1518	O	TRP	A	184	34.791	17.353	17.913	1.00	42.88
ATOM	1519	CB	TRP	A	184	35.049	13.926	18.839	1.00	42.62
ATOM	1520	CG	TRP	A	184	35.075	14.460	20.253	1.00	39.47
ATOM	1521	CD1	TRP	A	184	34.123	15.236	20.830	1.00	37.50
ATOM	1522	CD2	TRP	A	184	36.109	14.271	21.216	1.00	41.84
ATOM	1523	NE1	TRP	A	184	34.491	15.541	22.123	1.00	36.00
ATOM	1524	CE2	TRP	A	184	35.717	14.963	22.380	1.00	39.37
ATOM	1525	CE3	TRP	A	184	37.328	13.587	21.201	1.00	39.30
ATOM	1526	CZ2	TRP	A	184	36.504	14.983	23.529	1.00	41.08
ATOM	1527	CZ3	TRP	A	184	38.105	13.599	22.341	1.00	41.95

ATOM	1528	CH2	TRP	A	184	37.692	14.293	23.486	1.00	42.37
ATOM	1529	N	GLU	A	185	33.292	15.809	17.270	1.00	42.34
ATOM	1530	CA	GLU	A	185	32.211	16.770	17.099	1.00	42.70
ATOM	1531	C	GLU	A	185	30.950	16.204	17.765	1.00	43.74
ATOM	1532	O	GLU	A	185	30.589	15.062	17.506	1.00	43.14
ATOM	1533	CB	GLU	A	185	31.903	17.074	15.635	1.00	42.03
ATOM	1534	CG	GLU	A	185	33.023	17.900	14.999	1.00	38.91
ATOM	1535	CD	GLU	A	185	32.851	18.134	13.528	1.00	42.12
ATOM	1536	OE1	GLU	A	185	31.953	17.527	12.910	1.00	40.53
ATOM	1537	OE2	GLU	A	185	33.641	18.955	13.015	1.00	39.53
ATOM	1538	N	VAL	A	186	30.374	17.021	18.653	1.00	43.76
ATOM	1539	CA	VAL	A	186	29.211	16.563	19.400	1.00	43.51
ATOM	1540	C	VAL	A	186	27.943	17.165	18.791	1.00	45.37
ATOM	1541	O	VAL	A	186	27.804	18.379	18.647	1.00	43.51
ATOM	1542	CB	VAL	A	186	29.339	17.008	20.872	1.00	41.67
ATOM	1543	CG1	VAL	A	186	28.159	16.494	21.688	1.00	41.68
ATOM	1544	CG2	VAL	A	186	30.697	16.596	21.452	1.00	34.89
ATOM	1545	N	HIS	A	187	27.012	16.272	18.454	1.00	46.62
ATOM	1546	CA	HIS	A	187	25.679	16.656	18.003	1.00	50.05
ATOM	1547	C	HIS	A	187	24.620	16.257	19.023	1.00	52.23
ATOM	1548	O	HIS	A	187	24.447	15.055	19.262	1.00	52.60
ATOM	1549	CB	HIS	A	187	25.329	15.949	16.672	1.00	51.22
ATOM	1550	CG	HIS	A	187	26.356	16.159	15.600	1.00	53.27
ATOM	1551	ND1	HIS	A	187	26.135	16.916	14.467	1.00	55.72
ATOM	1552	CD2	HIS	A	187	27.633	15.710	15.495	1.00	54.05
ATOM	1553	CE1	HIS	A	187	27.216	16.925	13.713	1.00	49.24
ATOM	1554	NE2	HIS	A	187	28.134	16.205	14.329	1.00	53.78
ATOM	1555	N	ALA	A	188	23.836	17.199	19.524	1.00	54.61
ATOM	1556	CA	ALA	A	188	22.883	16.882	20.591	1.00	57.68
ATOM	1557	C	ALA	A	188	21.502	17.477	20.393	1.00	59.90
ATOM	1558	O	ALA	A	188	20.747	17.673	21.356	1.00	60.86
ATOM	1559	CB	ALA	A	188	23.501	17.291	21.929	1.00	57.50
ATOM	1560	N	GLY	A	189	21.107	17.773	19.155	1.00	61.42
ATOM	1561	CA	GLY	A	189	19.809	18.381	18.867	1.00	62.45
ATOM	1562	C	GLY	A	189	19.862	19.892	18.710	1.00	62.76
ATOM	1563	O	GLY	A	189	18.863	20.613	18.809	1.00	63.40
ATOM	1564	N	GLY	A	190	21.051	20.429	18.448	1.00	62.37
ATOM	1565	CA	GLY	A	190	21.211	21.883	18.338	1.00	60.60
ATOM	1566	C	GLY	A	190	22.551	22.159	17.660	1.00	58.62
ATOM	1567	O	GLY	A	190	23.029	21.274	16.958	1.00	58.39
ATOM	1568	N	GLN	A	191	23.173	23.285	17.983	1.00	56.77
ATOM	1569	CA	GLN	A	191	24.466	23.554	17.336	1.00	54.69
ATOM	1570	C	GLN	A	191	25.462	22.451	17.687	1.00	52.57
ATOM	1571	O	GLN	A	191	25.599	22.082	18.858	1.00	52.69
ATOM	1572	CB	GLN	A	191	24.972	24.927	17.760	1.00	58.35
ATOM	1573	CG	GLN	A	191	26.437	25.200	17.502	1.00	62.97
ATOM	1574	CD	GLN	A	191	26.166	26.948	17.561	0.00	99.00
ATOM	1575	OE1	GLN	A	191	25.459	27.683	16.891	0.00	99.00
ATOM	1576	NE2	GLN	A	191	27.070	27.403	18.451	0.00	99.00
ATOM	1577	N	VAL	A	192	26.162	21.943	16.684	1.00	49.07
ATOM	1578	CA	VAL	A	192	27.264	21.012	16.898	1.00	45.59
ATOM	1579	C	VAL	A	192	28.237	21.647	17.875	1.00	44.47
ATOM	1580	O	VAL	A	192	28.473	22.853	17.803	1.00	45.15
ATOM	1581	CB	VAL	A	192	27.960	20.717	15.544	1.00	42.50
ATOM	1582	CG1	VAL	A	192	29.047	19.665	15.684	1.00	39.90
ATOM	1583	CG2	VAL	A	192	26.874	20.237	14.584	1.00	40.84
ATOM	1584	N	ILE	A	193	28.831	20.882	18.775	1.00	41.81
ATOM	1585	CA	ILE	A	193	29.875	21.406	19.636	1.00	39.71
ATOM	1586	C	ILE	A	193	31.246	21.009	19.127	1.00	40.00
ATOM	1587	O	ILE	A	193	31.569	19.822	19.009	1.00	40.12
ATOM	1588	CB	ILE	A	193	29.715	20.868	21.104	1.00	36.14
ATOM	1589	CG1	ILE	A	193	28.303	21.218	21.573	1.00	38.63
ATOM	1590	CG2	ILE	A	193	30.765	21.585	21.957	1.00	38.85

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ATOM   1591  CD1 ILE A 193      27.916  20.591  22.922  1.00 41.29
ATOM   1592  N   LEU A 194      32.075  22.008  18.852  1.00 39.67
ATOM   1593  CA  LEU A 194      33.436  21.783  18.388  1.00 40.23
ATOM   1594  C   LEU A 194      34.455  21.944  19.486  1.00 40.97
ATOM   1595  O   LEU A 194      34.136  22.489  20.557  1.00 40.07
ATOM   1596  CB  LEU A 194      33.741  22.794  17.252  1.00 38.19
ATOM   1597  CG  LEU A 194      32.736  22.764  16.101  1.00 42.91
ATOM   1598  CD1 LEU A 194      33.203  23.702  14.980  1.00 42.33
ATOM   1599  CD2 LEU A 194      32.593  21.362  15.514  1.00 41.05
ATOM   1600  N   CYS A 195      35.658  21.430  19.269  1.00 41.29
ATOM   1601  CA  CYS A 195      36.711  21.575  20.273  1.00 43.15
ATOM   1602  C   CYS A 195      36.956  23.045  20.562  1.00 45.32
ATOM   1603  O   CYS A 195      37.083  23.872  19.671  1.00 44.47
ATOM   1604  CB  CYS A 195      37.981  20.893  19.785  1.00 44.75
ATOM   1605  SG  CYS A 195      39.358  21.057  20.920  1.00 43.19
ATOM   1606  N   PRO A 196      36.918  23.423  21.847  1.00 46.44
ATOM   1607  CA  PRO A 196      36.978  24.814  22.245  1.00 47.49
ATOM   1608  C   PRO A 196      38.376  25.335  22.514  1.00 48.05
ATOM   1609  O   PRO A 196      38.575  26.531  22.759  1.00 49.91
ATOM   1610  CB  PRO A 196      36.123  24.820  23.515  1.00 48.09
ATOM   1611  CG  PRO A 196      36.293  23.449  24.079  1.00 47.48
ATOM   1612  CD  PRO A 196      36.834  22.513  23.018  1.00 47.09
ATOM   1613  N   THR A 197      39.365  24.477  22.488  1.00 48.20
ATOM   1614  CA  THR A 197      40.753  24.821  22.766  1.00 49.51
ATOM   1615  C   THR A 197      41.610  24.697  21.491  1.00 48.70
ATOM   1616  O   THR A 197      41.132  24.143  20.508  1.00 47.51
ATOM   1617  CB  THR A 197      41.337  23.819  23.789  1.00 54.19
ATOM   1618  OG1 THR A 197      42.063  22.755  23.133  1.00 60.20
ATOM   1619  CG2 THR A 197      40.249  23.146  24.620  1.00 60.00
ATOM   1620  N   SER A 198      42.874  25.104  21.600  1.00 48.43
ATOM   1621  CA  SER A 198      43.755  25.011  20.443  1.00 49.41
ATOM   1622  C   SER A 198      44.106  23.572  20.088  1.00 51.13
ATOM   1623  O   SER A 198      44.340  22.748  20.974  1.00 50.32
ATOM   1624  CB  SER A 198      45.022  25.837  20.600  1.00 41.67
ATOM   1625  OG  SER A 198      44.689  27.176  20.863  1.00 42.21
ATOM   1626  N   VAL A 199      44.135  23.321  18.783  1.00 51.78
ATOM   1627  CA  VAL A 199      44.448  22.018  18.210  1.00 54.21
ATOM   1628  C   VAL A 199      45.846  22.063  17.593  1.00 55.85
ATOM   1629  O   VAL A 199      46.229  23.043  16.958  1.00 55.32
ATOM   1630  CB  VAL A 199      43.415  21.673  17.105  1.00 55.83
ATOM   1631  CG1 VAL A 199      43.848  20.450  16.311  1.00 58.48
ATOM   1632  CG2 VAL A 199      42.081  21.363  17.794  1.00 58.90
ATOM   1633  N   PHE A 200      46.643  21.031  17.823  1.00 57.80
ATOM   1634  CA  PHE A 200      48.033  20.977  17.458  1.00 60.84
ATOM   1635  C   PHE A 200      48.501  19.863  16.538  1.00 63.34
ATOM   1636  O   PHE A 200      47.988  18.771  16.373  1.00 63.71
ATOM   1637  CB  PHE A 200      48.976  20.962  18.695  1.00 56.48
ATOM   1638  CG  PHE A 200      49.009  22.350  19.286  1.00 51.93
ATOM   1639  CD1 PHE A 200      49.867  23.304  18.779  1.00 50.53
ATOM   1640  CD2 PHE A 200      48.118  22.686  20.298  1.00 52.06
ATOM   1641  CE1 PHE A 200      49.844  24.596  19.289  1.00 48.79
ATOM   1642  CE2 PHE A 200      48.104  23.972  20.813  1.00 46.67
ATOM   1643  CZ  PHE A 200      48.952  24.921  20.283  1.00 48.73
ATOM   1644  N   SER A 201      49.612  20.201  15.906  1.00 65.54
ATOM   1645  CA  SER A 201      50.520  19.367  15.151  1.00 67.49
ATOM   1646  C   SER A 201      50.543  17.927  15.652  1.00 68.56
ATOM   1647  O   SER A 201      50.873  17.710  16.841  1.00 69.46
ATOM   1648  CB  SER A 201      51.928  19.984  15.374  1.00 69.06
ATOM   1649  OG  SER A 201      51.799  21.376  15.666  1.00 64.56
ATOM   1650  OT  SER A 201      50.201  17.025  14.856  1.00 71.71
ATOM   1651  OW0 WAT W   1      16.850   8.350  41.749  1.00 33.70
ATOM   1652  OW0 WAT W   2      14.700   3.706  36.739  1.00 34.70
ATOM   1653  OW0 WAT W   3      23.512 -21.581  45.725  1.00 35.04
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ATOM	1654	OW0	WAT	W	4	13.647	-16.192	51.826	1.00	35.32
ATOM	1655	OW0	WAT	W	5	27.151	6.021	35.728	1.00	35.70
ATOM	1656	OW0	WAT	W	6	35.841	19.641	17.028	1.00	36.41
ATOM	1657	OW0	WAT	W	7	12.924	7.105	31.382	1.00	36.46
ATOM	1658	OW0	WAT	W	8	22.396	20.058	35.878	1.00	36.81
ATOM	1659	OW0	WAT	W	9	17.562	-18.568	44.759	1.00	38.24
ATOM	1660	OW0	WAT	W	10	23.931	7.992	29.610	1.00	38.55
ATOM	1661	OW0	WAT	W	11	32.085	22.981	25.237	1.00	38.76
ATOM	1662	OW0	WAT	W	12	18.237	6.493	43.333	1.00	38.96
ATOM	1663	OW0	WAT	W	13	19.973	21.293	36.711	1.00	38.84
ATOM	1664	OW0	WAT	W	14	14.757	-3.264	32.978	1.00	39.29
ATOM	1665	OW0	WAT	W	15	19.948	-2.552	48.084	1.00	39.94
ATOM	1666	OW0	WAT	W	16	13.394	-3.627	35.420	1.00	40.05
ATOM	1667	OW0	WAT	W	17	24.218	1.873	40.503	1.00	40.12
ATOM	1668	OW0	WAT	W	18	12.970	-9.846	41.166	1.00	40.24
ATOM	1669	OW0	WAT	W	19	29.332	23.835	36.728	1.00	40.10
ATOM	1670	OW0	WAT	W	20	32.982	14.615	37.196	1.00	40.03
ATOM	1671	OW0	WAT	W	21	15.963	-14.411	41.801	1.00	40.85
ATOM	1672	OW0	WAT	W	22	36.115	14.124	27.538	1.00	41.62
ATOM	1673	OW0	WAT	W	23	36.759	24.316	27.854	1.00	41.58
ATOM	1674	OW0	WAT	W	24	24.232	-12.120	40.700	1.00	41.18
ATOM	1675	OW0	WAT	W	25	20.170	8.808	43.184	1.00	41.55
ATOM	1676	OW0	WAT	W	26	14.174	8.391	52.525	1.00	43.14
ATOM	1677	OW0	WAT	W	27	25.412	3.713	30.549	1.00	41.48
ATOM	1678	OW0	WAT	W	28	14.723	-7.678	41.271	1.00	41.77
ATOM	1679	OW0	WAT	W	29	19.317	13.171	52.356	1.00	41.81
ATOM	1680	OW0	WAT	W	30	23.266	21.233	27.612	1.00	42.08
ATOM	1681	OW0	WAT	W	31	11.768	12.568	50.507	1.00	42.04
ATOM	1682	OW0	WAT	W	32	13.539	-13.131	41.639	1.00	42.18
ATOM	1683	OW0	WAT	W	33	11.508	10.524	52.379	1.00	42.93
ATOM	1684	OW0	WAT	W	34	3.363	-0.753	38.246	1.00	42.96
ATOM	1685	OW0	WAT	W	35	22.835	-3.224	40.382	1.00	43.01
ATOM	1686	OW0	WAT	W	36	26.824	22.825	28.526	1.00	43.00
ATOM	1687	OW0	WAT	W	37	18.644	-1.265	41.392	1.00	43.97
ATOM	1688	OW0	WAT	W	38	8.736	-6.966	49.493	1.00	43.69
ATOM	1689	OW0	WAT	W	39	15.651	-14.676	38.985	1.00	43.87
ATOM	1690	OW0	WAT	W	40	8.333	-12.297	37.586	1.00	44.06
ATOM	1691	OW0	WAT	W	41	25.939	7.843	39.161	1.00	44.11
ATOM	1692	OW0	WAT	W	42	10.384	9.683	30.485	1.00	44.27
ATOM	1693	OW0	WAT	W	43	0.943	8.083	43.152	1.00	44.34
ATOM	1694	OW0	WAT	W	44	21.071	2.692	43.998	1.00	44.65
ATOM	1695	OW0	WAT	W	45	16.203	7.540	48.658	1.00	44.83
ATOM	1696	OW0	WAT	W	46	21.491	-11.431	40.332	1.00	44.88
ATOM	1697	OW0	WAT	W	47	21.292	-1.593	41.871	1.00	45.24
ATOM	1698	OW0	WAT	W	48	33.051	8.145	30.148	1.00	45.89
ATOM	1699	OW0	WAT	W	49	11.644	15.303	50.268	1.00	46.78
ATOM	1700	OW0	WAT	W	50	35.864	19.699	14.264	1.00	46.41
ATOM	1701	OW0	WAT	W	51	7.067	6.695	50.824	1.00	46.58
ATOM	1702	OW0	WAT	W	52	27.033	16.432	44.207	1.00	47.45
ATOM	1703	OW0	WAT	W	53	12.107	-10.902	38.882	1.00	47.44
ATOM	1704	OW0	WAT	W	54	31.232	24.588	19.293	1.00	47.66
ATOM	1705	OW0	WAT	W	55	21.781	-3.130	44.031	1.00	47.48
ATOM	1706	OW0	WAT	W	56	7.169	-27.314	41.711	1.00	48.17
ATOM	1707	OW0	WAT	W	57	33.861	-1.778	23.374	1.00	48.53
ATOM	1708	OW0	WAT	W	58	33.357	8.082	26.362	1.00	48.51
ATOM	1709	OW0	WAT	W	59	26.396	24.163	13.998	1.00	49.70
ATOM	1710	OW0	WAT	W	60	21.233	20.044	43.429	1.00	49.73
ATOM	1711	OW0	WAT	W	61	39.604	24.739	18.318	1.00	49.28
ATOM	1712	OW0	WAT	W	62	24.974	-18.827	45.601	1.00	50.87
ATOM	1713	OW0	WAT	W	63	21.207	-0.654	31.876	1.00	49.81
ATOM	1714	OW0	WAT	W	64	13.203	8.179	28.792	1.00	50.30
ATOM	1715	OW0	WAT	W	65	21.887	5.385	43.977	1.00	50.58
ATOM	1716	OW0	WAT	W	66	24.468	6.206	27.276	1.00	50.23

ATOM	1717	OW0	WAT	W	67	16.159	-6.928	39.274	1.00	50.79
ATOM	1718	OW0	WAT	W	68	18.759	17.803	28.696	1.00	50.80
ATOM	1719	OW0	WAT	W	69	13.821	14.472	25.933	1.00	52.01
ATOM	1720	OW0	WAT	W	70	5.992	2.145	50.465	1.00	52.52
ATOM	1721	OW0	WAT	W	71	22.450	0.866	42.331	1.00	52.86
ATOM	1722	OW0	WAT	W	72	37.480	14.455	29.856	1.00	52.16
ATOM	1723	OW0	WAT	W	73	7.914	14.799	34.609	1.00	52.26
ATOM	1724	OW0	WAT	W	74	33.074	14.728	12.928	1.00	52.80
ATOM	1725	OW0	WAT	W	75	-2.139	5.177	35.817	1.00	53.07
ATOM	1726	OW0	WAT	W	76	8.849	6.339	29.567	1.00	53.08
ATOM	1727	OW0	WAT	W	77	2.499	9.596	40.507	1.00	53.22
ATOM	1728	OW0	WAT	W	78	8.453	-4.313	50.928	1.00	53.22
ATOM	1729	OW0	WAT	W	79	13.988	-16.279	37.477	1.00	54.52
ATOM	1730	OW0	WAT	W	80	29.311	23.613	25.169	1.00	53.94
ATOM	1731	OW0	WAT	W	81	10.698	17.607	37.556	1.00	53.87
ATOM	1732	OW0	WAT	W	82	10.533	-28.803	42.420	1.00	54.34
ATOM	1733	OW0	WAT	W	83	1.674	-0.659	35.990	1.00	54.11
ATOM	1734	OW0	WAT	W	84	13.238	5.649	29.129	1.00	54.35
ATOM	1735	OW0	WAT	W	85	23.172	23.184	42.047	1.00	53.98
ATOM	1736	OW0	WAT	W	86	25.591	-14.157	41.467	1.00	54.33
ATOM	1737	OW0	WAT	W	87	39.505	4.678	27.285	1.00	55.10
ATOM	1738	OW0	WAT	W	88	33.071	24.177	22.504	1.00	53.92
ATOM	1739	OW0	WAT	W	89	2.865	-14.306	47.361	1.00	55.09
ATOM	1740	OW0	WAT	W	90	10.824	5.199	27.990	1.00	54.87
ATOM	1741	OW0	WAT	W	91	13.268	-18.762	37.013	1.00	55.07
ATOM	1742	OW0	WAT	W	92	19.672	23.135	34.883	1.00	56.03
ATOM	1743	OW0	WAT	W	93	3.899	3.408	32.498	1.00	56.24
ATOM	1744	OW0	WAT	W	94	17.326	5.781	50.106	1.00	56.35
ATOM	1745	OW0	WAT	W	95	46.420	28.753	20.001	1.00	56.50
ATOM	1746	OW0	WAT	W	96	18.033	-25.950	38.021	1.00	56.78
ATOM	1747	OW0	WAT	W	97	16.668	11.173	20.729	1.00	57.28
ATOM	1748	OW0	WAT	W	98	-0.327	-1.130	37.865	1.00	56.31
ATOM	1749	OW0	WAT	W	99	13.791	-29.887	42.473	1.00	56.28
ATOM	1750	OW0	WAT	W	100	14.138	-6.120	36.256	1.00	56.78
ATOM	1751	OW0	WAT	W	101	-0.503	-1.004	43.200	1.00	56.68
ATOM	1752	OW0	WAT	W	102	7.034	2.268	29.920	1.00	57.78
ATOM	1753	OW0	WAT	W	103	39.612	16.983	21.840	1.00	57.56
ATOM	1754	OW0	WAT	W	104	12.322	-7.683	34.772	1.00	57.82
ATOM	1755	OW0	WAT	W	105	21.186	21.778	39.197	1.00	58.10
ATOM	1756	OW0	WAT	W	106	25.213	27.127	14.493	1.00	58.04
ATOM	1757	OW0	WAT	W	107	37.189	5.450	11.613	1.00	58.31
ATOM	1758	OW0	WAT	W	108	25.799	-17.600	47.916	1.00	58.58
ATOM	1759	OW0	WAT	W	109	25.505	0.503	36.518	1.00	57.70
ATOM	1760	OW0	WAT	W	110	21.154	19.292	24.315	1.00	58.80
ATOM	1761	OW0	WAT	W	111	23.932	23.123	29.269	1.00	58.45
ATOM	1762	OW0	WAT	W	112	30.025	16.034	12.701	1.00	58.92
ATOM	1763	OW0	WAT	W	113	5.440	-12.369	36.445	1.00	60.00
ATOM	1764	OW0	WAT	W	114	45.949	18.908	19.720	1.00	59.22
ATOM	1765	OW0	WAT	W	115	3.882	16.171	43.893	1.00	59.38
ATOM	1766	OW0	WAT	W	116	26.040	-17.629	41.513	1.00	58.92
ATOM	1767	OW0	WAT	W	117	13.942	-10.256	37.298	1.00	60.39
ATOM	1768	OW0	WAT	W	118	7.840	10.062	31.734	1.00	60.14
ATOM	1769	OW0	WAT	W	119	-1.860	-20.559	43.212	1.00	60.45
ATOM	1770	OW0	WAT	W	120	18.311	16.851	47.879	1.00	60.32
ATOM	1771	OW0	WAT	W	121	38.093	15.693	26.658	1.00	61.27
ATOM	1772	OW0	WAT	W	122	7.557	-26.418	44.769	1.00	61.39
ATOM	1773	OW0	WAT	W	123	17.200	-4.612	32.783	1.00	60.41
ATOM	1774	OW0	WAT	W	124	33.055	9.791	13.378	1.00	61.34
ATOM	1775	OW0	WAT	W	125	29.579	10.149	37.422	1.00	60.84
ATOM	1776	OW0	WAT	W	126	26.196	13.297	42.367	1.00	60.80
ATOM	1777	OW0	WAT	W	127	23.556	-4.737	42.642	1.00	61.18
ATOM	1778	OW0	WAT	W	128	10.687	-3.375	35.374	1.00	61.88
ATOM	1779	OW0	WAT	W	129	13.030	-13.947	38.339	1.00	62.52

ATOM	1780	OW0	WAT	W	130	9.747	-0.992	36.212	1.00	59.32
ATOM	1781	OW0	WAT	W	131	24.814	-11.997	45.661	1.00	62.19
ATOM	1782	OW0	WAT	W	132	23.200	4.574	23.546	1.00	61.90
ATOM	1783	OW0	WAT	W	133	24.938	30.370	17.496	1.00	62.23
ATOM	1784	OW0	WAT	W	134	35.459	1.260	16.603	1.00	62.66
ATOM	1785	OW0	WAT	W	135	24.178	20.068	20.090	1.00	61.73
ATOM	1786	OW0	WAT	W	136	40.127	0.350	18.771	1.00	62.44
ATOM	1787	OW0	WAT	W	137	19.279	14.663	46.778	1.00	63.59
ATOM	1788	OW0	WAT	W	138	20.090	20.354	46.023	1.00	62.81
ATOM	1789	OW0	WAT	W	139	15.250	18.974	46.516	1.00	63.68
ATOM	1790	OW0	WAT	W	140	21.267	-25.030	39.386	1.00	63.31
ATOM	1791	OW0	WAT	W	141	26.107	2.756	33.033	1.00	63.89
ATOM	1792	OW0	WAT	W	142	13.216	16.259	48.398	1.00	64.51
ATOM	1793	OW0	WAT	W	143	23.474	19.596	51.112	1.00	65.45
ATOM	1794	OW0	WAT	W	144	6.778	10.141	28.981	1.00	64.57
ATOM	1795	OW0	WAT	W	145	23.613	15.848	49.685	1.00	64.50
ATOM	1796	OW0	WAT	W	146	21.834	-6.518	36.556	1.00	65.24
ATOM	1797	OW0	WAT	W	147	10.139	-10.444	36.806	1.00	65.85
ATOM	1798	OW0	WAT	W	148	32.489	10.232	33.677	1.00	64.60
ATOM	1799	OW0	WAT	W	149	31.655	6.263	27.510	1.00	64.29
ATOM	1800	OW0	WAT	W	150	4.585	-20.934	39.031	1.00	66.94
ATOM	1801	OW0	WAT	W	151	38.484	11.674	18.085	1.00	65.84
ATOM	1802	OW0	WAT	W	152	42.438	8.992	21.219	1.00	65.71
ATOM	1803	OW0	WAT	W	153	33.971	24.173	27.259	1.00	66.15
ATOM	1804	OW0	WAT	W	154	24.597	-9.268	45.286	1.00	67.06
ATOM	1805	OW0	WAT	W	155	-2.112	-26.008	50.039	1.00	66.08
ATOM	1806	OW0	WAT	W	156	9.030	-32.481	39.896	1.00	66.14
ATOM	1807	OW0	WAT	W	157	-3.216	-18.835	45.004	1.00	67.94
ATOM	1808	OW0	WAT	W	158	-3.398	4.020	40.260	1.00	65.32
ATOM	1809	OW0	WAT	W	159	25.878	24.231	20.622	1.00	68.10
ATOM	1810	OW0	WAT	W	160	27.187	4.546	24.805	1.00	67.75
ATOM	1811	OW0	WAT	W	161	24.071	24.303	35.784	1.00	67.51
ATOM	1812	OW0	WAT	W	162	7.746	17.585	52.663	1.00	70.19
ATOM	1813	OW0	WAT	W	163	19.301	4.980	47.873	1.00	68.23
ATOM	1814	OW0	WAT	W	164	10.439	-4.135	32.539	1.00	65.45
ATOM	1815	OW0	WAT	W	165	23.798	-0.930	41.113	1.00	68.64
ATOM	1816	OW0	WAT	W	166	2.464	5.318	30.549	1.00	65.77
ATOM	1817	OW0	WAT	W	167	9.665	-14.876	35.700	1.00	65.21
ATOM	1818	OW0	WAT	W	168	1.759	10.431	44.227	1.00	69.25
ATOM	1819	OW0	WAT	W	169	20.960	4.214	26.258	1.00	69.97
ATOM	1820	OW0	WAT	W	170	28.769	24.807	27.878	1.00	67.86
ATOM	1821	OW0	WAT	W	171	30.212	14.473	8.293	1.00	69.23
ATOM	1822	OW0	WAT	W	172	20.178	0.312	50.589	1.00	70.29
ATOM	1823	OW0	WAT	W	173	19.736	6.852	23.117	1.00	70.72
ATOM	1824	OW0	WAT	W	174	8.978	16.807	50.514	1.00	70.10
ATOM	1825	OW0	WAT	W	175	25.144	-1.759	34.429	1.00	71.96
ATOM	1826	OW0	WAT	W	176	26.946	25.298	35.563	1.00	68.69
ATOM	1827	OW0	WAT	W	177	44.918	5.619	13.054	1.00	70.16
ATOM	1828	OW0	WAT	W	178	22.370	24.094	38.170	1.00	71.66
ATOM	1829	OW0	WAT	W	179	-0.624	10.187	33.201	1.00	72.23
ATOM	1830	OW0	WAT	W	180	11.015	17.856	47.520	1.00	71.42
ATOM	1831	OW0	WAT	W	181	7.766	0.898	52.950	1.00	71.64
ATOM	1832	OW0	WAT	W	182	3.469	-28.368	52.511	1.00	70.10

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Claims

1. A crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof, comprising residues vital for transcriptional and replicational activities of said protein.

2. An E2NT dimer protein according to Claim 1 wherein the residues lie on opposite sides of an N-terminal domain.

3. An E2NT dimer protein according to either preceding claim wherein the residues comprise a plurality of residue clusters associated with a structural role at an interface between N1 and N2 terminal domains of respective monomers within the dimer.

4. An E2NT dimer according to Claim 3 comprising three clusters.

5. An E2NT dimer according to either of Claims 3 or 4 wherein a first cluster of vital residues is associated with interactions between N1 and N2 domains and comprises any one or more of the following residues Ile82, Glu90, Trp92, Lys112, Tyr138, Val145.

6. An E2NT dimer according to any one of Claims 3-5 wherein a second cluster of residues is associated with N1 interactions and comprises either or both of residues Trp33 and Leu94.

7. An E2NT dimer according to any one of Claims 3-6 wherein a third cluster of residues is associated with N2 interactions and comprises any one or more of the following residues Pro106, Lys111, Phe168, Trp134.

8. An E2NT dimer according to any preceding claim further comprising residues associated with transactivation and/or replication properties of E2.

9. An E2NT dimer according to Claim 8 wherein the residues comprise any one or more of the following residues Glu20, Glu100, Asp122, Arg37, Glu39, Ile73, Gln12 and Ala69.

10. Use of a crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein according to any preceding claim or homologue thereof in mapping mutations onto an E2 three-dimensional structure so as to identify areas of amino acid conservation and the effect of mutations on folding of the E2 protein.

11. Use according to Claim 10 in rationalised antiviral drug design.

12. An *in vitro* method for identifying and/or selecting a candidate therapeutic agent, the method comprising determining interaction of a E2 N-terminal module (E2NT) dimer in a sample by contacting said sample with said candidate therapeutic agent and measuring DNA loop formation in E2.

13. Use of the method according to Claim 12 in identifying and/or selecting an antiviral candidate therapeutic agent.

14. Use according to Claim 13 wherein identification/selection of the candidate therapeutic agent depends on its ability to interfere with or block interactions of E2NT so as to interfere or block viral and/or cellular transcription factors.

15. Use of an E2NT dimerisation inhibitor for the preparation of a medicament for treatment of conditions that arise as a result of HPV infection.

16. Use according to Claim 15 for the treatment of warts, proliferative skin lesions and/or cervical cancer.

17. A method of monitoring the efficacy of an antiviral therapy in a patient receiving a medicament for the treatment of an HPV infection comprising taking a sample from said patient and measuring E2NT interactions and/or DNA loop formation.

18. Use of a dimerisation surface of an crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein or homologue thereof according to any one of Claims 1-9 as a target site for interaction with putative antiviral agents and/or for measuring efficacy of said agents.

19. A method for identifying and/or selecting a candidate therapeutic agent, comprising applying rationalised drug design to a crystal structure obtainable by crystallising E2NT, cryogenically freezing the crystals and generating the crystal structure using X-ray diffraction.

20. A method of claim 19, wherein the method by which the E2NT crystal structure is obtainable comprises crystallisation using hanging-drop vapour diffusion.

21. A method of claim 19 or claim 20 wherein the method by which E2NT crystal structure is obtainable comprises X-ray diffraction using uranium acetate and gold cyanide E2NT derivatives and refining with data extending to 1.9 Å spacing.

22. A method of any of claims 19 to 21, wherein the crystal structure comprises the portions of amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94.

23. A method of any of claims 19 to 22, wherein the rationalised drug design comprises designing drugs which interact with the dimerisation surface of E2NT.

24. A computer for producing a three-dimensional representation of a molecule or molecular complex, wherein said molecule or molecular complex comprises or a

three-dimensional representation of a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, wherein said computer comprises:

(a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises the structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3;

(b) a working memory for storing instructions for processing said machine-readable data;

(c) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said three-dimensional representation; and

(d) a display coupled to said central-processing unit for displaying said three-dimensional representation.

25. The computer according to claim 24, wherein said three-dimensional representation is of a molecule or molecular complex is defined by the set of structure coordinates according to Table 3, or wherein said three-dimensional representation is of a homologue of said molecule or molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

26. A computer for determining at least a portion of the structure coordinates corresponding to an X-ray diffraction pattern of a molecule or molecular complex, wherein said computer comprises:

(a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises at least a portion of the structural coordinates according to Table 3;

(b) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises an X-ray diffraction pattern of said molecule or molecular complex;

(c) a working memory for storing instructions for processing said machine-readable data of (a) and (b);

(d) a central-processing unit coupled to said working memory and to said machine-readable data storage medium of (a) and (b) for performing a Fourier transform of the machine readable data of (a) and for processing said machine readable data of (b) into structure coordinates; and

(e) a display coupled to said central-processing unit for displaying said structure coordinates of said molecule or molecular complex.

27. A crystallised molecule or molecular complex comprising a dimerisation surface defined by structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

28. The crystallized molecule or molecular complex according to claim 27, wherein said molecule or molecular complex is defined by the set of structure coordinates according to Table 3, or a homologue thereof, wherein said homologue has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

29. A machine-readable data storage medium, comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of a molecule or molecular complex comprising a dimerisation surface defined by structure coordinates of E2NT amino acids Ile82, Glu90, Trp92, Lys112, Tyr138, Val145, Pro106, Lys111, Phe168, Trp134, Trp33 and Leu94 according to Table 3, or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

30. The machine-readable data storage medium according to claim 7, wherein said molecule or molecular complex is defined by the set of structure coordinates according to Table 3, or a homologue of said molecule or molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

31. A machine-readable data storage medium comprising a data storage material encoded with a first set of machine readable data which, when combined with a second set of machine readable data, using a machine programmed with instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data, wherein: said first set of data comprises a Fourier transform of at least a portion of the structural coordinates according to Table 3; and said second set of data comprises an x-ray diffraction pattern of a molecule or molecular complex.

32. A method for evaluating the ability of a chemical entity to associate with a molecule or molecular complex according to claim 27 or claim 28 comprising the steps of:

a. employing computational means to perform a fitting operation between the chemical entity and a dimerisation surface of the molecule or molecular complex; and

b. analysing the results of said fitting operation to quantify the association between the chemical entity and the dimerisation surface.

33. A drug or therapeutic agent identified, assessed or selected using a crystallised molecular complex of an E2NT protein or its crystal structure or using a complex of any of claims 1 to 9, a method of claim 12, a use of any of claims 13, claim 14 or 18. a method of any of claims 20 to24 or 32 or a product of any of claims 25 to 31.

FIG. 1. A

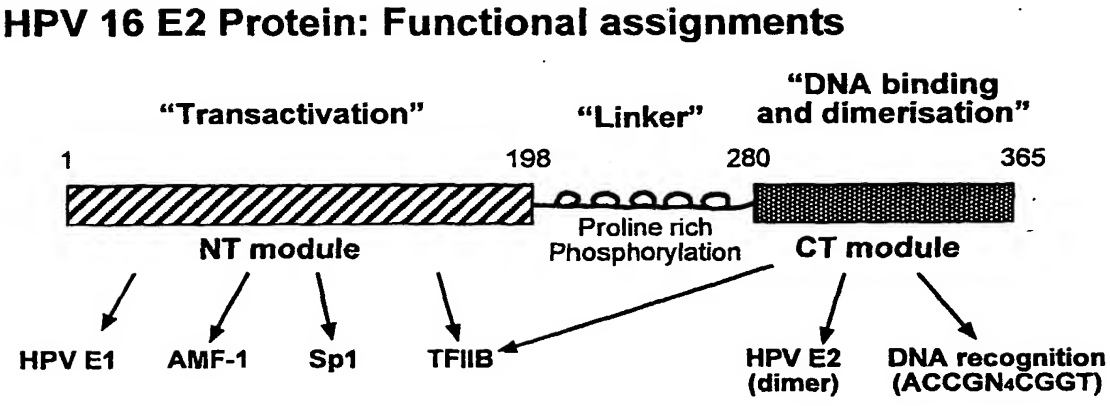

HPV 16 E2 Protein: Functional assignments
"Transactivation"
"Linker"
"DNA binding and dimerisation"
1
198
280
365
Proline rich Phosphorylation
NT module
CT module
HPV E1
AMF-1
Sp1
TFIIB
HPV E2 (dimer)
DNA recognition (ACCGN4CGGT)

Fig. 1.B

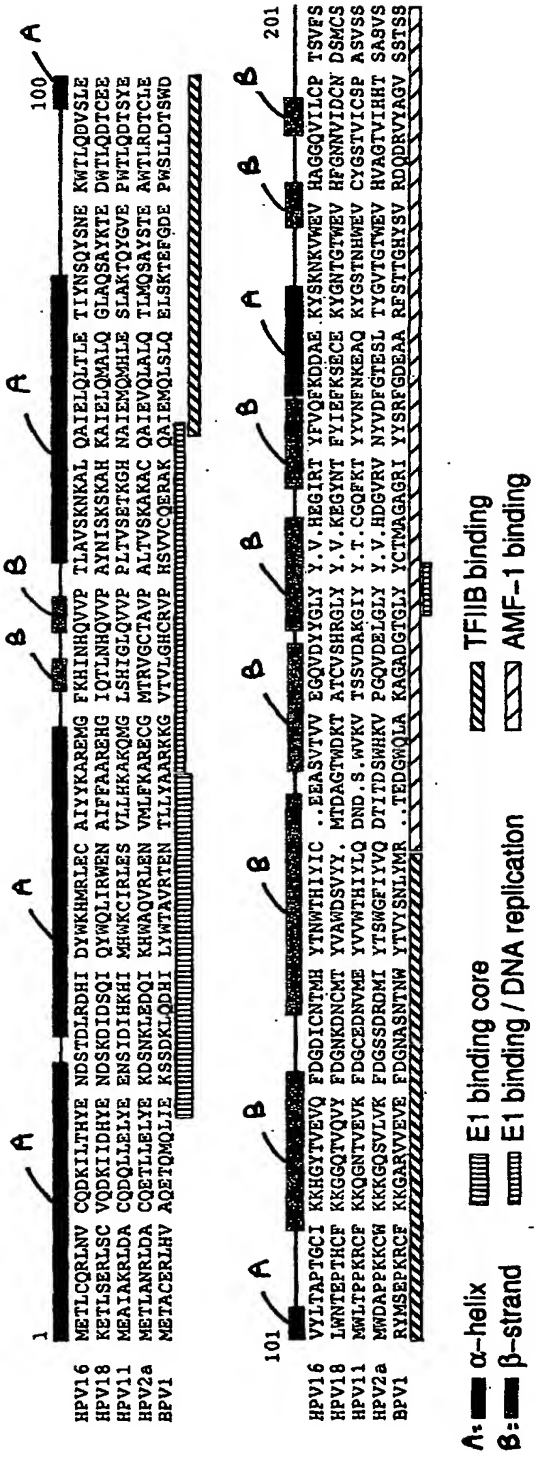
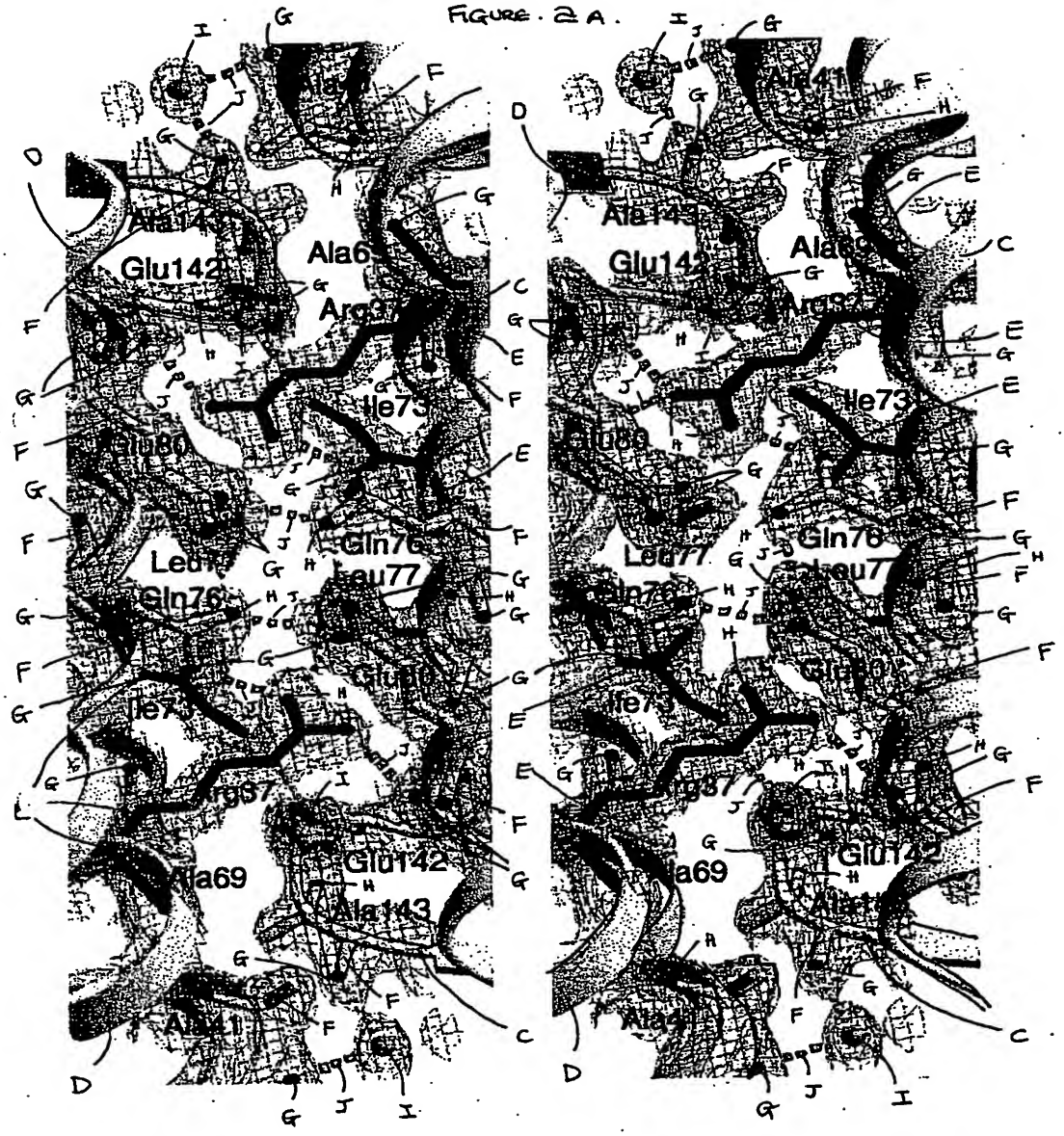
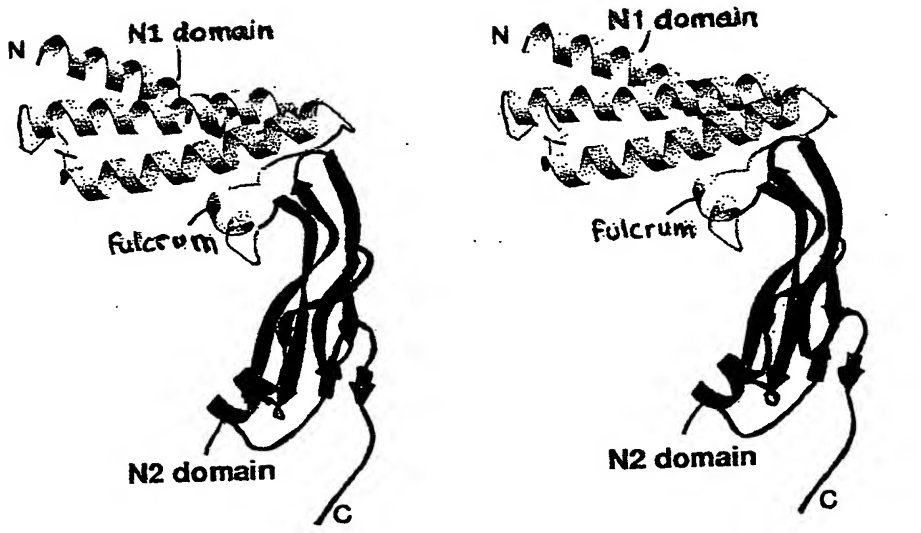

HPV16 METLCQRLNV CQDKILTHYE NDSTDLRDHI DYWKHMRLEC AIYYKAREMG FKHINHQVVP TLAVSKNKAL QAIELQLTLE TIYNSQYSNE KWTLQDVSLE
HPV18 KETLSERLSC VQDKIIDHYE NDSKDIDSQI QYWQLIRWEN AIFFAAREHG IQTLNHQVVP AYNISKSKAH KAIELQMALQ GLAQSAYKTE DWTLQDTCEE
HPV11 MEAIAKRLDA CQDQLLELYE ENSIDIHKHI MHWKCIRLES VLLHKAKQMG LSHIGLQVVP PLTVSETKGH NAIEMQMHLE SLAKTQYGVE PWTLQDTSYE
HPV2a METLANRLDA CQETLLELYE KDSNKLEDQI KHWAQVRLEN VMLFKARECG MTRVGCTAVP ALTVSKAKAC QAIEVQLALQ TLMQSAYSTE AWTLRDTCLE
BPV1 METACERLHV AQETQMQLIE KSSDKLQDHI LYWTAVRTEN TLLYAARKKG VTVLGHCRVP HSVVCQERAK QAIEMQLSLQ ELSKTEFGDE PWSLLDTSWD
HPV16 VYLTAPTGCI KKHGYTVEVQ FDGDICNTMH YTNWTHIYIC ..EEASVTVV EGQVDYYGLY Y.V.HEGIRT YFVQFKDDAE KYSKNKVWEV HAGGQVILCP TSVFS
HPV18 LWNTEPTHCF KKGGQTVQVY FDGNKDNCMT YVAWDSVYI. MTDAGTWDKT ATCVSHRGLY Y.V.KEGYNT FYIEFKSECE KYGNTGTWEV HFGNNVIDCN DSMCS
HPV11 MWLTPPKRCF KKQGNTVEVK FDGCEDNVME YVVWTHIYLQ DND.S.WVKV TSSVDAKGIY Y.T.CGQFKT YYVNFNKEAQ KYGSTNHWEV CYGSTVICSP ASVSS
HPV2a MWDAPPKKCW KKKGQSVLVK FDGSSDRDMI YTSWGFIYVQ DTITDSWHKV PGQVDELGLY Y.V.HDGVRV NYVDFGTESL TYGVTGTWEV HVAGTVIHHT SASVS
BPV1 RYMSEPKRCF KKGARVVEVE FDGNASNTNW YTVYSNLYMR ..TEDGWQLA KAGADGTGLY YCTMAGAGRI YYSRFGDEAA RFSTTGHYSV RDQDRVYAGV SSTSS
A: α-helix
B: β-strand
E1 binding core
E1 binding / DNA replication
TFIIB binding
AMF-1 binding

FIGURE. 2A.



[C= blue; monomer ribbon : D= yellow; monomer ribbon : E = dark green; side chains of Arg37 and Ile 73 ; F = light green; side chains of other residues: O = O_2; red : H = blue; N_2 ; I = orange H_2O: J = dashed sticks; hydrogen bonds]

FIGURE . 2B



N = N1 domain = aquamarine
M = fulcrum = green
L = N2 domain = pink

FIG. 2C

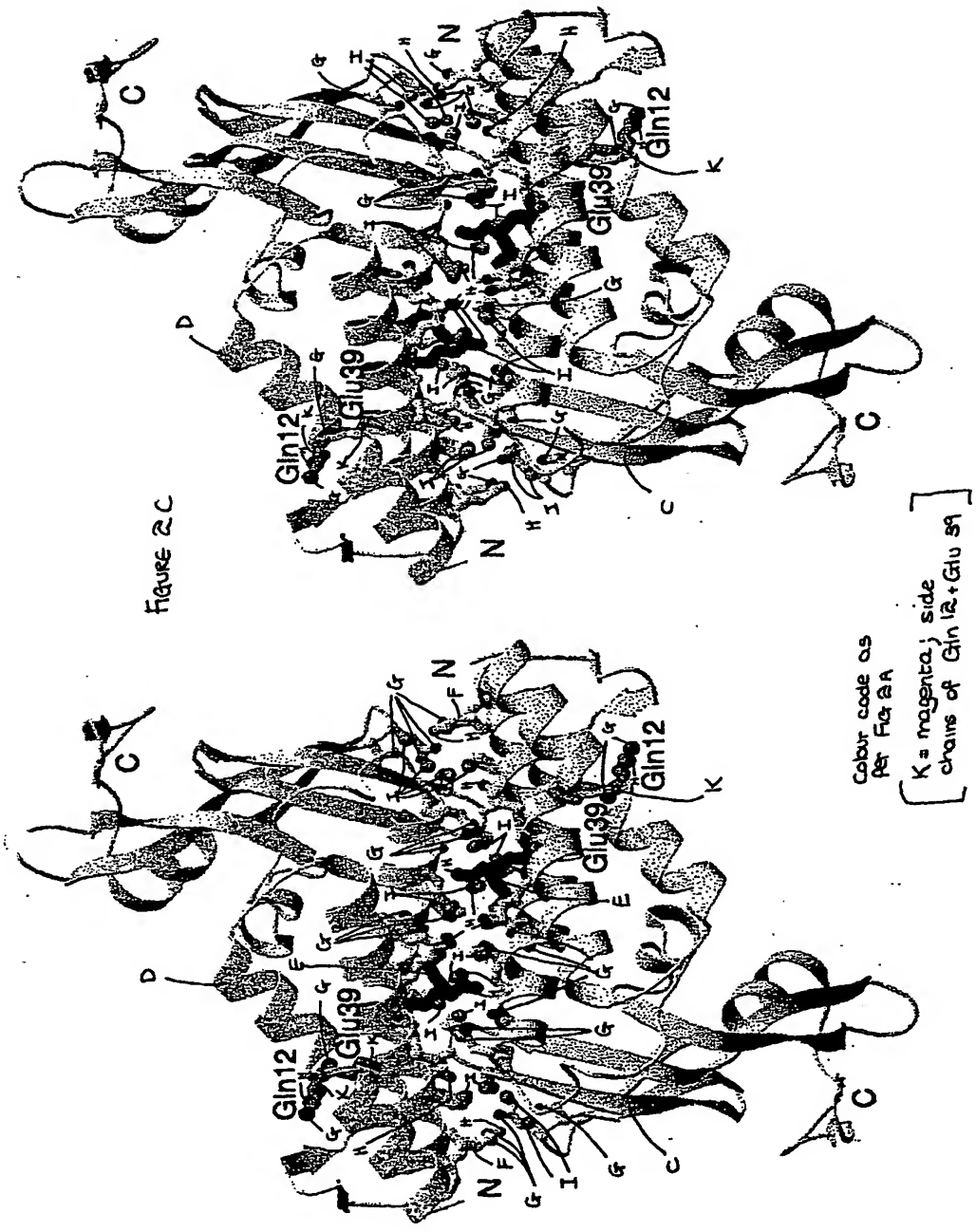


Figure 2C

Fig 3.A.

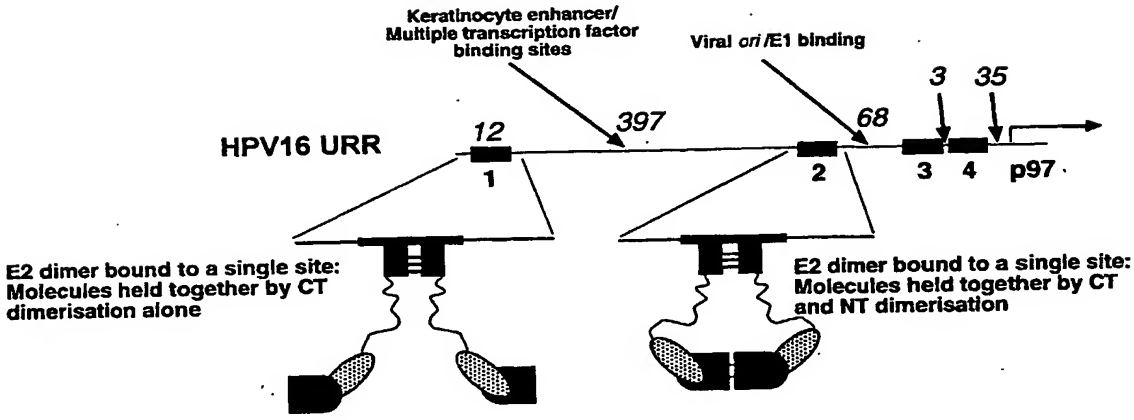

Keratinocyte enhancer/
Multiple transcription factor
binding sites
Viral ori/E1 binding
3
35
HPV16 URR
12
397
68
1
2
3
4
p97
E2 dimer bound to a single site:
Molecules held together by CT
dimerisation alone
E2 dimer bound to a single site:
Molecules held together by CT
and NT dimerisation

Fig. 3B

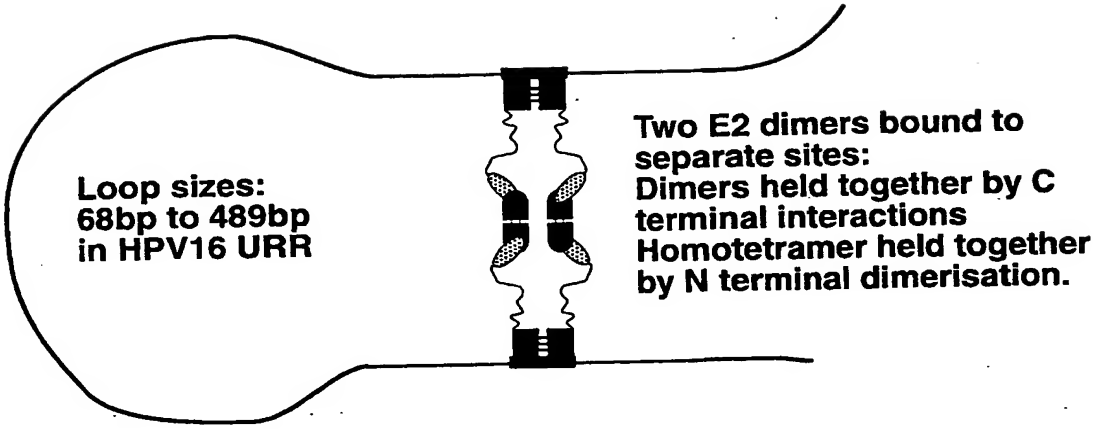

Loop sizes:
68bp to 489bp
in HPV16 URR
Two E2 dimers bound to
separate sites:
Dimers held together by C
terminal interactions
Homotetramer held together
by N terminal dimerisation.

FIG. 3.C

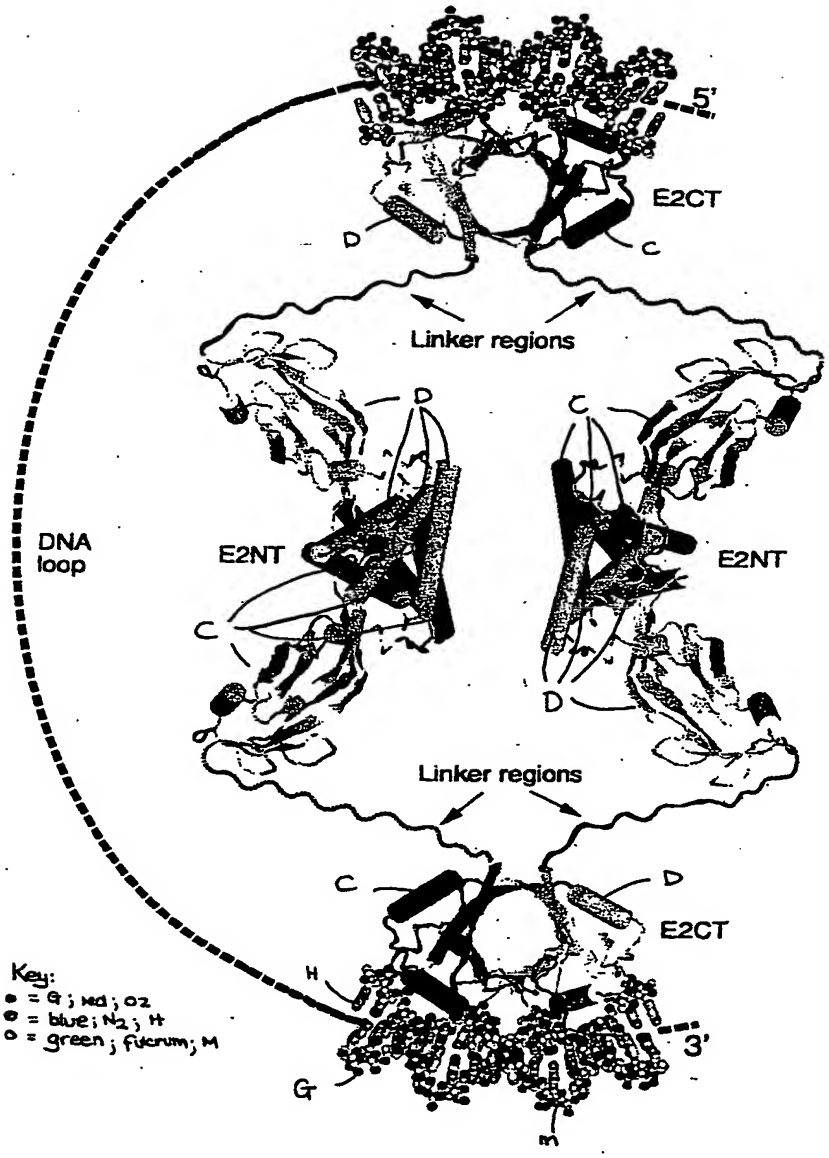

5'
E2CT
D
C
Linker regions
D
C
DNA
loop
E2NT
E2NT
C
D
Linker regions
C
D
E2CT
H
3'
G
m
Key:
● = G; Md; O2
● = blue; N2; H
○ = green; fulcrum; M

Fig. 3.D

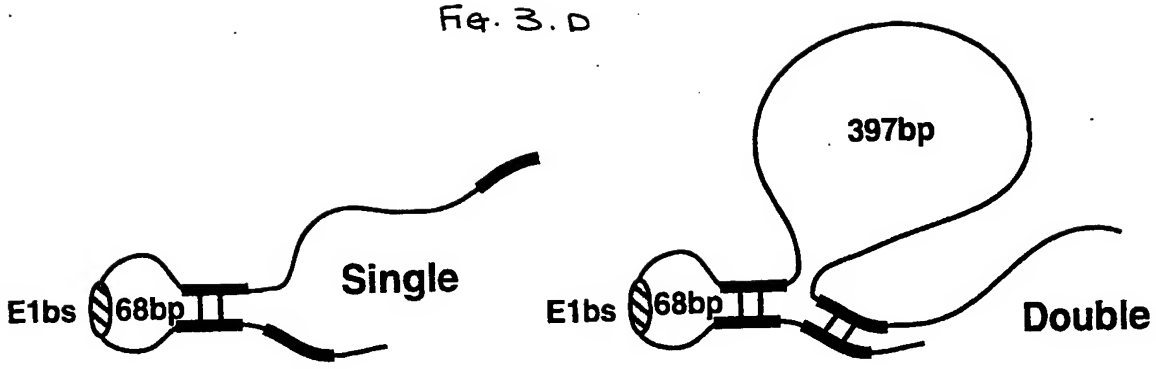
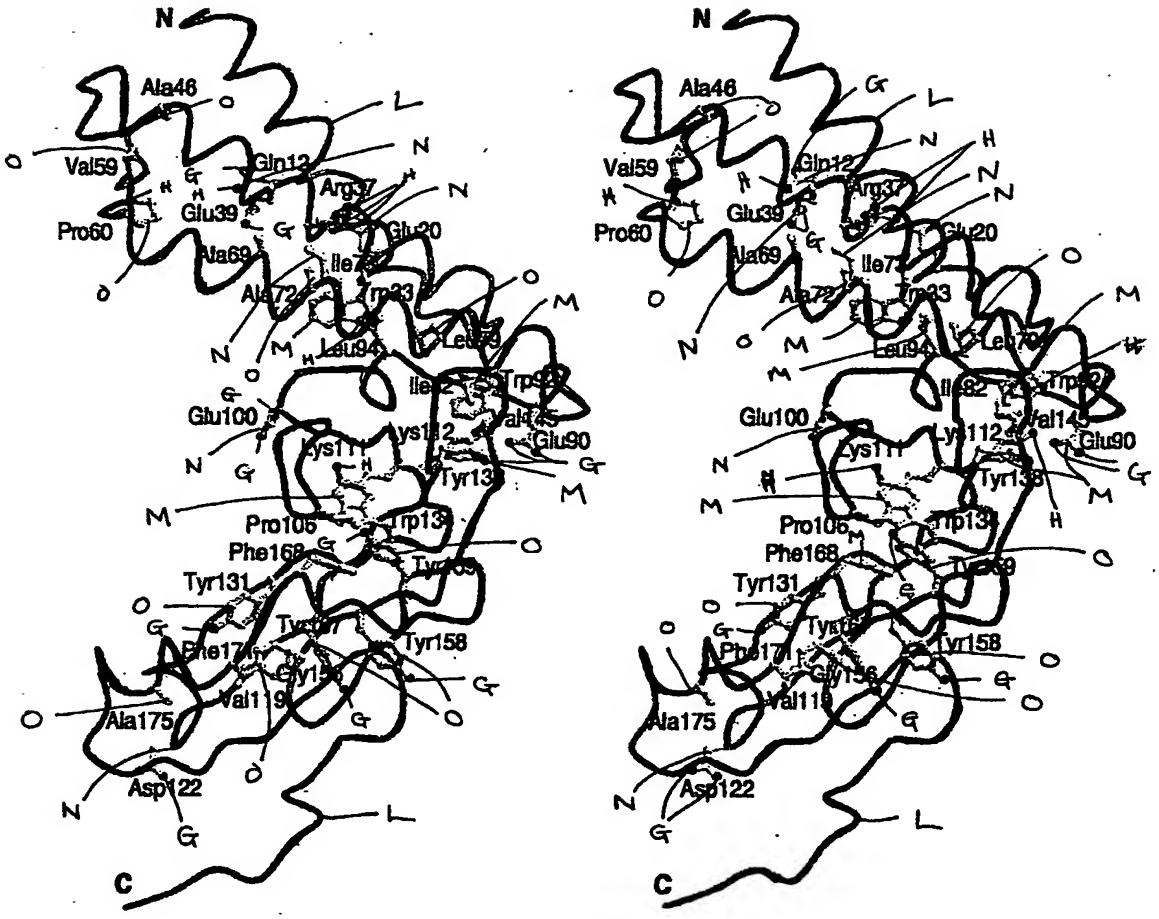


FIG. 4A.



O = yellow; sulphur atoms.

Fig. 4.B

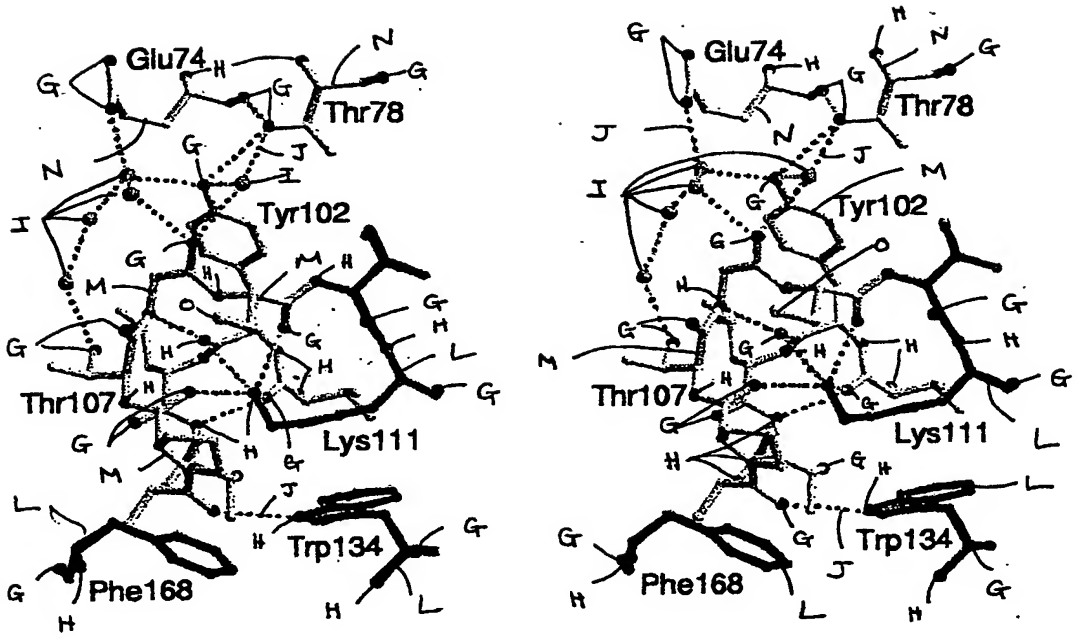
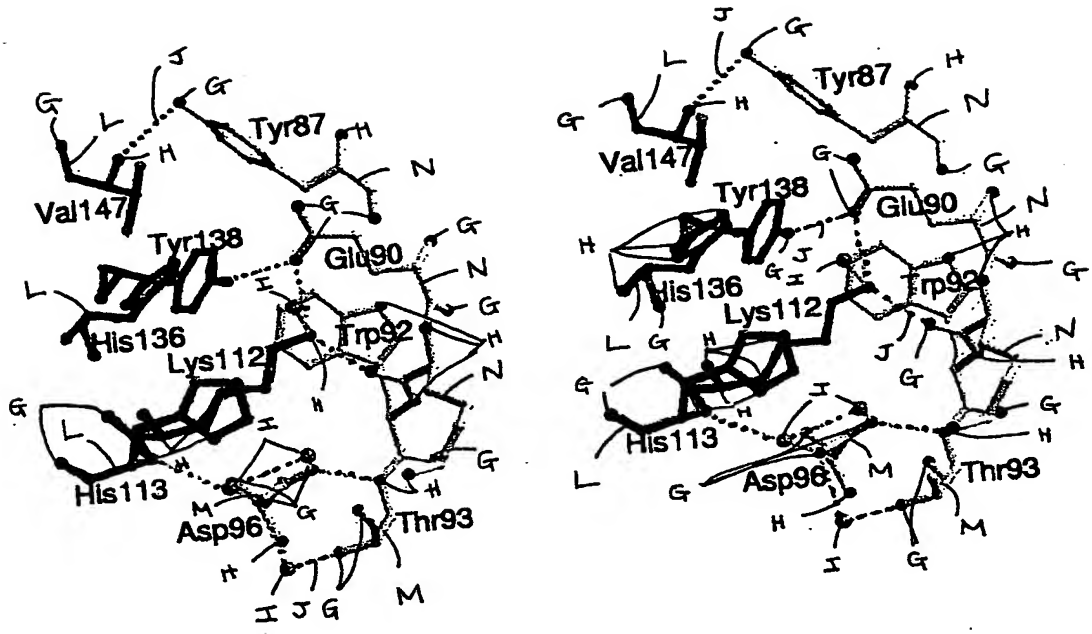
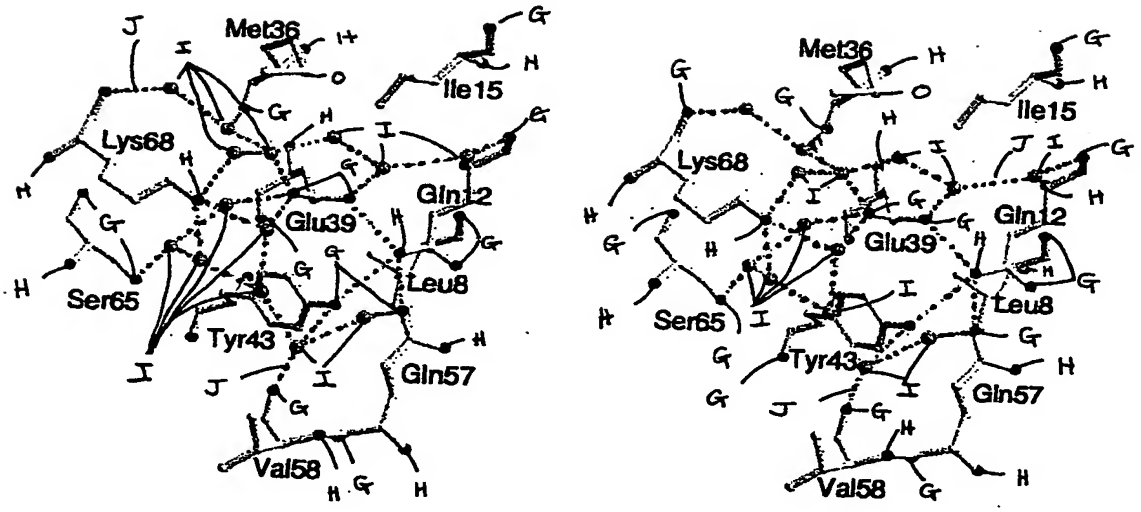

Glu74
Thr78
Tyr102
Thr107
Lys111
Trp134
Phe168
Glu74
Thr78
Tyr102
Thr107
Lys111
Trp134
Phe168

FIG. 4C


Tyr87
Val147
Tyr138
Glu90
His136
Lys112
Trp92
His113
Asp96
Thr93

Fieure 4D.


Met36
Ile15
Lys68
Glu39
Gln12
Ser65
Leu8
Tyr43
Gln57
Val58
Met36
Ile15
Lys68
Glu39
Gln12
Ser65
Leu8
Tyr43
Gln57
Val58

TENT COOPERATION TREA

PCT

REC'D 17 JAN 2002
WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
LPB/P32059WO		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB00/03568	18/09/2000	17/09/1999
International Patent Classification (IPC) or national classification and IPC C07K14/00		
Applicant THE UNIVERSITY OF YORK et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 7 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☒ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
17/04/2001	17.01.2002
Name and mailing address of the international preliminary examining authority: *European Patent Office* D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Marinoni, J-C Telephone No. +49 89 2399 8563

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB00/03568

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-66 as originally filed

Claims, No.:

1-31 with telefax of 23/11/2001

Drawings, sheets:

1/13-13/13 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

II. Priority

1. ☐ This report has been established as if no priority had been claimed due to the failure to furnish within the prescribed time limit the requested:

☐ copy of the earlier application whose priority has been claimed.

☐ translation of the earlier application whose priority has been claimed.

2. ☐ This report has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid.

Thus for the purposes of this report, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:
see separate sheet

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 23-25 and 28-30, all completely.

because:

☒ the said international application, or the said claims Nos. 23-25 and 28-30, all completely relate to the following subject matter which does not require an international preliminary examination (*specify*):
see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☒ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion

could be formed.

☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-22, 26, 27, 31
	No:	Claims	None
Inventive step (IS)	Yes:	Claims	None
	No:	Claims	1-22, 26, 27, 31
Industrial applicability (IA)	Yes:	Claims	1-22, 26, 27, 31
	No:	Claims	None

2. Citations and explanations
see separate sheet

Re Item I

Basis of the opinion

The amendments filed with the letter dated 23 November 2001 are considered to be formally allowable under Articles 19(2) and 34(2) PCT.

Re Item II

Priority

The claimed priority date appears to be valid. Therefore, the document Antson et al., NATURE, 17 February 2000, pages 805-809, which was cited as P,X by the ISA is not taken into account for the establishment of the present opinion.

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. **Claims 23-25 and 28-30** merely amount to the presentation of information. According to Rule 67.1(v) PCT, examination of such claims is not required.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The present application relates to crystals of a dimeric N-terminal domain of the Human Papillomavirus E2 activator (NT-HPVE2) type 18 and their use.

2. It is not at present clear what could form the technical problem underlying the present application which does not disclose how the crystals claimed are linked to an invention other than the mere recitation of the possible uses of said crystal. The resolution of a three-dimensional structure of a protein is *a priori* a scientific problem: space coordinates of a given protein constitute an admittedly complex parameter but still remain nothing else than physical parameters. As such, three-dimensional structure data do not automatically solve any technical problem, except if the determination of these data has produced a surprising technical

effect, *e.g.* if the methods based on this structure had provided a confirmed inhibitor/antagonist... In the absence of such a technical effect, it is concluded that the subject-matter of **claims 26 and 27** does not meet the requirements of Article 33(3) PCT concerning inventive step.

3. It appear also obvious that the skilled person would set out to crystallize a E2NT protein dimer and would succeed in doing so, since obtaining crystals of any protein is nowadays more or less straightforward. Crystals are usually and obviously obtained for use in rationalized drug design: since obtaining the crystals of the invention did not appear to involve overcoming a technical prejudice (and since the claims do not refer to a particular method overcoming this prejudice) **claims 1-22 and 31** are considered to merely recite what the skilled person would intend to do with said crystal(s). As such their subject-matter does not involve an inventive step and therefore does not meet the requirements of Article 33(3) PCT.

4. In other words, **claims 1-22 and 31** are directed to uses and methods which have not been put into practice successfully within the limits of the invention or which refer to unclear or even undisclosed matter (like undefined "dimerisation surface"): their subject-matter merely amounts to the wording of the technical problem to be solved which does not involve an inventive step *per se* (Articles 6 and 33(3) PCT; see also the Guidelines of the PCT, Ch. III, 4.7).

Claims

1. Use, in rationalised drug design, of a crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein, the E2NT dimer protein comprising residues at its dimer interface that are vital for transcriptional and replicational activities of said protein and wherein the residues comprise any one or more of the following residues Glu20, Glu100, Asp122, Arg37, Glu39, Ile73, Gln12 and Ala69.

2. Use of protein according to Claim 1 wherein the residues lie on opposite sides of an N-terminal domain.

3. Use of a protein according to either preceding claim wherein the residues comprise a plurality of further residue clusters associated with a structural role at an interface between N1 and N2 terminal domains of respective monomers within the dimer.

4. Use of a protein according to Claim 3 wherein the E2NT dimer protein comprises three clusters.

5. Use of a protein according to either of Claims 3 or 4 wherein a first cluster of vital residues is associated with interactions between N1 and N2 domains and comprises any one or more of the following residues Ile82, Glu90, Trp92, Lys112, Tyr138, Val145.

6. Use of a protein according to any one of Claims 3 to5 wherein a second cluster of residues is associated with N1 interactions and comprises either or both of residues Trp33 and Leu94.

7. Use of a protein according to any one of Claims 3 to 6 wherein a third cluster of residues is associated with N2 interactions and comprises any one or more of the following residues Pro106, Lys111, Phe168, Trp134.

8. Use of a protein according to any preceding claim wherein the crystallised molecular complex of the E2NT dimer protein is cryogenically frozen.

9. Use in mapping mutations onto an E2 three-dimensional structure so as to identify areas of amino acid conservation and/or the effect of mutations on folding of the E2 protein of a crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein, the E2NT dimer protein comprising residues at its dimer interface that are vital for transcriptional and replicational activities of said protein and wherein the residues comprise any one or more of the following residues Glu20, Glu100, Asp122, Arg37, Glu39, Ile73, Gln12 and Ala69..

10. Use of a protein according to claim 9 further including any one or more of the features receited in claims 2 to 8.

11. An *in vitro* method for identifying and/or selecting a candidate therapeutic agent, the method comprising the steps of

(i) determining interaction in a sample of a E2 N-terminal module (E2NT) dimer, the dimer comprising residues at its dimer interface that are vital for transcriptional and replicational activities of said protein and wherein the residues comprise any one or more of the following residues Glu20, Glu100, Asp122, Arg37, Glu39, Ile73, Gln12 and Ala69

(ii) contacting the sample with the candidate therapeutic agent and;

(iii) measuring DNA loop formation in E2.

12. A method according to claim 11 wherein the candidate therapeutic agent is for the treatment of warts, proliferative skin lesions and/or cervical cancer.

13. A method according to either claim 11 or 12 further including any one or more of the features receited in claims 2 to 8.

14. Use of the method according to any one of claims 10 to 13 in identifying and/or selecting an antiviral candidate therapeutic agent.

15. Use according to Claim 14 wherein identification/selection of the candidate therapeutic agent depends on its ability to interfere with or block interactions of E2NT so as to interfere or block viral and/or cellular transcription factors.

16. A method of monitoring the efficacy of an antiviral therapy in a patient receiving a medicament for the treatment of an HPV infection comprising the steps of:

(i) taking a sample from said patient

(ii) contacting the sample with an E2 N-terminal module (E2NT) dimer, the dimer comprising residues at its dimer interface that are vital for transcriptional and replicational activities of said protein and wherein the residues comprise any one or more of the following residues Glu20, Glu100, Asp122, Arg37, Glu39, Ile73, Gln12 and Ala69 and;

(iii) measuring E2NT interactions and/or DNA loop formation of the dimer.

17. Use of a dimerisation surface of an crystallised molecular complex of an E2 N-terminal module (E2NT) dimer protein according to any one of Claims 1-8 as a target site for interaction with putative antiviral agents and/or for measuring efficacy of said agents.

18. A method for identifying and/or selecting a candidate therapeutic agent, comprising applying rationalised drug design to a crystal structure obtainable by crystallising E2NT, cryogenically freezing the crystals and generating the crystal structure using X-ray diffraction the crystallised E2NT comprising residues at its dimer interface that are vital for transcriptional and replicational activities and wherein the residues comprise any one or more of the following residues Glu20, Glu100, Asp122, Arg37, Glu39, Ile73, Gln12 and Ala69.

19. A method of claim 18, wherein the method by which the E2NT crystal structure is obtainable comprises crystallisation using hanging-drop vapour diffusion.

20. A method of claim 18 or 19 wherein the method by which E2NT crystal structure is obtainable comprises X-ray diffraction using uranium acetate and gold cyanide E2NT derivatives and refining with data extending to 1.9 Å spacing.

21. A method of any of claims 18 to 20 further including any one or more of the features receited in claims 2 to 8..

22. A method of any of claims 18 to 21, wherein the rationalised drug design comprises designing drugs which interact with the dimerisation surface of E2NT.

23. A computer for producing a three-dimensional representation of a molecule or molecular complex, wherein said molecule or molecular complex comprises or a three-dimensional representation of a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å, wherein said computer comprises:

(a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises the structure coordinates of E2NT amino acids Glu20, Glu100, Asp122, Arg37, Glu39, Ile73, Gln12 and Ala69;

(b) a working memory for storing instructions for processing said machine-readable data;

(c) a central-processing unit coupled to said working memory and to said machine-readable data storage medium for processing said machine readable data into said three-dimensional representation; and

(d) a display coupled to said central-processing unit for displaying said three-dimensional representation.

24. The computer according to claim 23, wherein said three-dimensional representation is of a molecule or molecular complex is defined by the set of structure coordinates according to Table 3, or wherein said three-dimensional representation is of a homologue of said molecule or molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5 Å.

25. A computer for determining at least a portion of the structure coordinates corresponding to an X-ray diffraction pattern of a molecule or molecular complex, wherein said computer comprises:

(a) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises at least a portion of the structural coordinates according to Table 3;

(b) a machine-readable data storage medium comprising a data storage material encoded with machine-readable data, wherein said data comprises an X-ray diffraction pattern of said molecule or molecular complex;

(c) a working memory for storing instructions for processing said machine-readable data of (a) and (b);

(d) a central-processing unit coupled to said working memory and to said machine-readable data storage medium of (a) and (b) for performing a Fourier transform of the

machine readable data of (a) and for processing said machine readable data of (b) into structure coordinates; and

(e) a display coupled to said central-processing unit for displaying said structure coordinates of said molecule or molecular complex.

26. A crystallised molecule or molecular complex comprising a dimerisation surface defined by structure coordinates of E2NT amino acids Glu20, Glu100, Asp122, Arg37, Glu39, Ile73, Gln12 and Ala69 according to Table 3 or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

27. The crystallized molecule or molecular complex according to claim 26, wherein said molecule or molecular complex is defined by the set of structure coordinates according to Table 3, or a homologue thereof, wherein said homologue has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

28. A machine-readable data storage medium, comprising a data storage material encoded with machine readable data which, when using a machine programmed with instructions for using said data, is capable of displaying a graphical three-dimensional representation of a molecule or molecular complex comprising a dimerisation surface defined by structure coordinates of E2NT amino acids Glu20, Glu100, Asp122, Arg37, Glu39, Ile73, Gln12 and Ala69 according to Table 3, or a homologue of said molecule or molecular complex, wherein said homologue comprises a binding pocket that has a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

29. The machine-readable data storage medium according to claim 28, wherein said molecule or molecular complex is defined by the set of structure coordinates

according to Table [redacted] or a homologue of said molecule or molecular complex, said homologue having a root mean square deviation from the backbone atoms of said amino acids of not more than 1.5Å.

30. A machine-readable data storage medium comprising a data storage material encoded with a first set of machine readable data which, when combined with a second set of machine readable data, using a machine programmed with instructions for using said first set of data and said second set of data, can determine at least a portion of the structure coordinates corresponding to the second set of machine readable data, wherein: said first set of data comprises a Fourier transform of at least a portion of the structural coordinates according to Table 3; and said second set of data comprises an x-ray diffraction pattern of a molecule or molecular complex.

31. A method for evaluating the ability of a chemical entity to associate with a molecule or molecular complex according to claim 26 or 27 comprising the steps of:

a. employing computational means to perform a fitting operation between the chemical entity and a dimerisation surface of the molecule or molecular complex; and

b. analysing the results of said fitting operation to quantify the association between the chemical entity and the dimerisation surface.